The evaluation of SPUR - a novel patient-reported outcome measure of medication adherence in patients diagnosed with chronic conditions

Joshua Sterling Wells

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School of Life Sciences, Pharmacy and Chemistry

Kingston University

London

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Abstract

Introduction Medicines are the most widely used intervention in healthcare. Despite this, many patients do not take their medicines as prescribed, referred to as medication non-adherence. Globally, non-adherence is estimated to cost health systems >£300Bn annually. Costs are typically associated with adverse drug reactions, treatment failure, and increasing healthcare utilisation, such as hospital admissions. As global life expectancy continues to rise, so do diagnoses of chronic conditions and subsequently, prescribing and long-term reliance on medicines. Several methods to measure adherence have been developed. Yet to date, no known model does so holistically, nor provides contextual information about patient behaviour that could help to develop interventions which reduce adherence-related risks. The aim of this research was to evaluate the validity of a novel patient-reported outcome measure (PROM) of medication adherence, SPUR, and determine its application in clinical practice to identify adherence-related risks, such as hospital admissions.

Methods A systematic review was conducted to explore the scope, validity, and reporting of PROMs of medication adherence in patients living with Type 2 Diabetes (T2D). Following this, a cross-sectional study to provide preliminary quantitative evidence of validity for the SPUR model in patients living with T2D using psychometric analysis was conducted. A subsequent cross-sectional study was conducted in patients diagnosed with Chronic Obstructive Pulmonary Disease (COPD) to examine the cross-cultural validity of SPUR in a new population. Finally, an observational study was undertaken over a 12-month period to examine the relationship between SPUR and the risk of general and early readmission (readmitted within 30 days) to hospital in patients living with T2D. Moreover, the three studies collected and examined associations between SPUR and socio-demographic/clinical factors in relation to adherence e.g., age and comorbidity, as well as implementing other PROM and objective measures of adherence for comparison against SPUR. All studies received ethical approval from both the university and national NHS ethics committees. Data were analysed in SPSS and Microsoft Excel.

Results The systematic review highlighted that PROMs were commonly reported without adequate evidence of validity. Furthermore, there was little uptake of standardised frameworks or methodologies to support the assessment or reporting of PROMs. In the initial cross-sectional study, preliminary psychometric analysis produced a more concise 27-item SPUR model (SPUR-27). SPUR-27 demonstrated strong early evidence for the reliability and superiority of a holistic PROM as the only model to significantly correlate with both objective measures of adherence included in the study, HbA_{1c} ($p<0.05$) and the Medication Possession Ratio (MPR) ($p<0.01$). Evidence of cross-cultural validity was also established in the COPD cohort. SPUR-27 demonstrated significant correlations with MPR ($p<0.01$) and could distinguish groups of patients based on their COPD symptom severity ($\chi 2 = 8.570$, $p<0.01$). The final observational study identified that a higher SPUR-27 score (increased adherence) was predictive of both a lower number of readmissions to hospital, as well as early readmissions, during the 12-month period of the study.

Conclusion These early results indicate that SPUR-27 is a reliable PROM of adherence with cross-cultural validity in different groups of patients. Moreover, SPUR-27 was significantly predictive of adherence-related outcomes, such as hospital admissions, that could be used to develop interventions.

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Awards

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Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations

Abbreviation	Full Description
AATD	Alpha-1 Antitrypsin Deficiency
ABQ	Adherence Barriers Questionnaire
ACL	Anterior Cruciate Ligament
ADR	Adverse Drug Reaction
AIC	Akaike's Information Criterion
AIMS	Arthritis Impact Measurement Scales
AML	Acute Myeloid Leukaemia
AOR	Adjusted Odds Ratio
ARMS	Adherence to Refills and Medication Scale
ART	Anti-Retroviral Therapy
AUC	Area Under the Curve
BBQ	Beliefs and Behaviour Questionnaire
BeMQ	Beliefs about Medicines Questionnaire
BMI	Body Mass Index
BMQ	Brief Medication Questionnaire
CAD	Coronary Artery Disease
CAT	COPD Assessment Test
CCA	Cross-cultural Adaptation
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
CHF	Chronic Heart Failure
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
COSMIN	COnsensus-based Standards for the selection of health status Measurement Instruments
CP	Community Pharmacists
CrI	Credible Interval
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTT	Classical Test Theory
CVD	Cardiovascular Disease
DAI	Drug-Attitude Inventory
DALYs	Disability Adjusted Life Years
DAMS	Diagnostic Adherence to Medication Scale
DCP	Diabetes Care Profile
DDP-4	Dipetidylpeptidase-4
DIF	Differential Item Functioning
DTSQ	Diabetes Treatment Satisfaction Questionnaire
EFA	Exploratory Factor Analysis
EMP	Electronic Medication Packaging
EPR	Electronic Patient Records
EQ-5D	EuroQol-5D
FACT	Functional Assessment of Cancer Therapy
FDA	Food & Drug Administration
FEV1	Forced Expiratory Volume in 1 Second
FEV1% Pred	Percentage Predicted FEV1
FEV1/FVC	Forced Expiratory Volume in 1 Second/Full Vital Capacity Ratio

FPG	Fasting Plasma Glucose
FVC	Full Vital Capacity
GBD	Global Burden of Disease
GCP	Good Clinical Practice
GCSE	General Certificate of Secondary Education
GDPR	General Data Protection Regulations
GFI	Goodness of Fit Index
GLP-1	Glucagon-like-peptide-1
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GRS	Genetic Risk Score
HBM	Health Belief Model
HCPs	Health Care Professionals
HER	Electronic Health Records
HFrEF	Heart Failure with reduced Ejection Fraction
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRA	Health Research Authority
HRQoL	Health-Related Quality of Life
IASc	Inhaler Adherence Score
IC	Internal Consistency
ICC	Intraclass Correlation Coefficients
ICS	Inhaled Corticosteroid
IHD	Ischaemic Heart Disease
IMD	Index of Multiple Deprivation
IR	Incidence Ratio
ISOQoL	International Society for Quality-of-Life Research
ITC	Item-Total Correlation
KMO	Kaiser-Meyer-Olkin
KOOS-4	Knee injury and Osteoarthritis Outcome Score 4
KU	Kingston University
LABA	Long-Acting Beta Agonist
LAMA	Long-Acting Muscarinic Antagonist
LIMOS	Lewisham Integrated Medicines Optimisation Service
LSOA	Lower Super Output Areas
LTOT	Long-term Oxygen Therapy
MA	Medication Adherence
MARS	Medication Adherence Rating Scale
MCPA	Monte Carlo Parallel Analysis
MEMS	Medication Events Monitoring Systems
MeSH	Medical Subject Headings
MGCFA	Multi-Group Confirmatory Factor Analysis
MMAS	Morisky Medication Adherence Scale
mMRC	modified Medical Research Council
MMSE	Mini Mental-State Examination
MO	Medicines Optimisation
MOE	Margin of Error
MPR	Medication Possession Ratio
MTA	Medication Treatment Adherence Scale

NEJM	New England Journal of Medicine
NFI	Normed Fit Index
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NNFI	Non-normed Fit Index
OAs	Oral Antiglycaemics
OR	Odds Ratio
PAF	Principle Axis Factoring
PAM	Patient Activation Measure
PCFA	Partial Confirmatory Factor Analysis
PDC	Proportion of Days Covered
PDEA4I	Phosphodiesterase Type-4 Inhibitor
PIS	Participant Information Sheet
PMR	Patient Medical Record
PMT	Protection Motivation Theory
PPI	Patient and Public Involvement
PREMs	Patient Reported Experience Measures
PrEP	Pre-Exposure Prophylaxis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PRO	Patient Reported Outcome
PROMs	Patient Reported Outcome Measures
RCT	Randomised Control Trial
REC	Research Ethics Committee
RFI	Relative Fit Index
RMSEA	Root Mean Square Error of Approximation
ROC	Receiver Operator Characteristic
RR	Relative Risk
SABA	Short-Acting Beta Agonist
SAMA	Short-Acting Muscarinic Antagonist
SCR	Summary Care Record
SCT	Social Cognitive Theory
SDSCA	Summary of Diabetes Self-Care Activities
SDSCA	Standard Deviation
SEAMS	Self-Efficacy for Appropriate Medicine Use Scale
SEM	Standard Error of Measurement
SEM	Structural Equation Modelling
SF-36	Short Form-36
SGLT2	Sodium-Glucose Type 2 Receptor
SIP	Sickness Impact Profile
SOP	Standard Operating Procedures
SPSS	Statistical Package for the Social Sciences
SPUR	Social Psychological Usage Rational
SR	Systematic Review
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
T1D	Type 1 Diabetes
T2D	Type 2 Diabetes
TMB	Theoretical Models of Behaviour
TPB	Theory of Planned Behaviour

UHL	University Hospital Lewisham
UK	United Kingdom
UN	United Nations
US	United States
VMATC	Validating a Medication Adherence Tool in COPD
VMATT2	Validating a Medication Adherence Tool in Type 2 Diabetes
WHO	World Health Organisation
WOS	Web of Science

"Someday…, we'll medicate human experience right out of the human experience." - *Dennis Lehane*

1.1 The Shifting Status of Medicines in Society

The official recorded history of medicines dates back as far as 1800 BC.[1] Since that time, medicines have become the most common therapeutic intervention in healthcare.[2] Yet, as society has continued to evolve, so has our relationship with medicines from several perspectives. Improvements in our knowledge and approach to public health over the last few centuries have contributed to significantly improved life expectancy across the globe. However, as a result we have also observed a larger proportion of the population that are older and increasingly diagnosed with chronic conditions.[3] This rise in chronic conditions is accompanied by increasing costs for healthcare providers to manage such complex patients, while also decreasing the quality of life for those diagnosed with one, or more commonly, multiple chronic conditions that may require several medicines or interventions.[4] One might question why with such advancements in our approach to healthcare in modern society are these problems still prevailing, particularly with the wide availability of medicines as a critical intervention. However, it's important to recognise that the relationship between prescribing medicines and their expected positive outcomes for both patients and healthcare providers is rarely linear. To better understand the relationship between patients and their medicines, it's important to first outline how such measures are defined.

1.1.1 Defining Medication-Taking Terminology

Several terms are used to describe the way in which patients take their medicines. "Medication Adherence" (MA) is most described as "The extent to which the patient's behaviour matches agreed recommendations from the prescriber".[5] This phrase is well adopted throughout the literature and used somewhat preferably in lieu of the term

"Medication Compliance", which is more commonly defined as "the extent to which the patient's behaviour matches the prescriber's recommendations". This shift is language also represents a shift in our perspective on prescribing and the role of the patient as a decision maker within the prescriber-patient dynamic. As highlighted by Gould and Mitty[6], compliance infers an element of dependency and does little to reflect a shared approach to decision making between patients and prescribers. The approach of shared decision making implies communication between patients and prescribers and this is a core component of the more recent concept, "Medication Concordance".[7] The latter term is suggested as an addition to MA, which looks to reflect the partnership between patients and prescribers, by including beliefs about medicines, particularly their perceived benefits and harms, as part of the patient-prescriber dynamic and decision-making process. Although these terms are used somewhat interchangeably, their use and evolution reflect a clear consensus that involving patients in their care is an increasingly essential and positive component of prescribing, particularly with a view to support medication-taking behaviour. For the purpose of this thesis, the term "Medication Adherence" (MA) was chosen and will be used hereafter.

1.1.2 Evolving Views on Medication Adherence

Describing the way in which patients may or may not take their medicines is an important first step in better understanding how to measure such behaviours. MA, as a facet of behavioural science, became more popularised in the late 1970s, which Trostle[8] attributes in part to the work of Haynes *et al*[9] who defined and coined the term "Medication Compliance" in 1979. During this time, clinicians had started to increasingly recognise the role of MA and its association with poorer patient outcomes, such as failure to attend appointments, elevated rates of medicines-related harm, and overall treatment failure with newly prescribed drug regimens.[10] This shifting perception of MA and its role in patient care was particularly true for people diagnosed with chronic conditions as highlighted by German in 1988.[10] In fact,

German describes the "salience" of the conversation at the time, given that the shifting population demographic had led to an increase in patients diagnosed with chronic conditions. This was inadvertently met with an increasing need to develop new ways to manage these more complex patients. From this work, early estimates for MA rates of patients living with chronic conditions became more widely reported throughout the 1980s – Becker[11] highlights that only 50% of patients with a chronic condition were determined to be adherent to their medicines based on evidence provided by clinical studies available at that time.

1.1.3 Describing Medication Adherence Behaviour

The factors that drive patient behaviour around taking their medicines are myriad and personal to each patient. However, two of the more traditional umbrella terms to describe these facets of behaviour are intentional and unintentional medication non-adherence. The former is indicative of an active decision to not take one's medicines for a variety of reasons, whereas the latter may be more reflective of demographics, such as age, or one's clinical condition, as emphasised by Wroe.[12] Intentional non-adherence behaviour may be propagated by specific beliefs about medicines such as expected harm or adverse effects associated with a treatment, a perceived lack of efficacy, or a reluctance or failure to recognise the necessity of a treatment.[13–15] Furthermore, the extent to which a patient may exhibit intentional non-adherence may be directly and positively influenced by the relationship with their prescriber(s). Specifically, even small adjustments to the way in which a prescriber communicates with a patient by removing medical terminology and focusing on the patient's vocabulary have demonstrated improvements in patient satisfaction and treatment outcomes, including intentional non-adherence.[16] Conversely, unintentional non-adherence is not an active decision but may instead be the result of forgetfulness, a language barrier, or functional disability as few examples of contributing factors.[17–20] Although unintentional and intentional non-adherence are often described in contrast, works by Lehane and McCarthy[20] reflect on

the potential overlap between the two facets of behaviour and the need for a more comprehensive model of describing MA. Although earlier discussions have positioned intentional non-adherence as directly related to cognition and beliefs about medicines, delineating it from unintentional non-adherence may not be as clear cut as previously described.[12] For example, a cross-sectional study of adults living with chronic conditions (n=24,017) identified that beliefs about medicines were also predictive of unintentional non-adherence in addition to intentional non-adherence.[21] Similarly, in a study conducted by Lowry *et al*,[22] patients (n=588) with diagnosed hypertension that experienced adverse drug reactions (ADRs), such as wheezing or frequent urination, were significantly more likely to report intentional and unintentional non-adherence in tandem. Race as a socio-demographic factor was also significantly associated with both types of non-adherence in bivariate analysis,[22] however socio-demographics had previously only been attributed to unintentional non-adherence. Whilst the binary definition of non-adherence has demonstrated evidence as a useful framework for describing patient behaviour, there is still a considerable lack of clinically and cost-effective MA interventions that have been derived from this concept.[20] When attempting to aggregate such personal and diverse behaviours into two large and distinct subgroups, we may fail to address the complex interplay and overlap of drivers and factors that impact MA, particularly among patients with chronic conditions where MA interventions have demonstrated limited clinical efficacy.[23,24] Therefore, before exploring MA behaviour and measures in more detail, the following sections will provide a background on the evolution of chronic conditions and their impact on MA as we look to discuss the developments and challenges associated with addressing MA behaviour.

1.2 Ageing & the Burden of Chronic Conditions

Notably, estimates provided some 40 years later for MA rates among patients living with chronic conditions have not changed since some of the earliest reports in the 1980s. In fact, in

2011 the World Health Organisation (WHO) reported the same estimate of approximately 50% of people living with chronic conditions to be non-adherent to their medicines. However, one apparent and significant shift since the 1980s is both the large growth in global population size and the resulting health and economic burden associated with the rising prevalence of chronic conditions and as a result, medicines use. United Nations (UN) figures report a global population of approximately 4.45Bn people as of 1980, however this is in stark contrast to the UN's most recent report that puts the global population at 8Bn people as of November 15th, 2022.[25,26]

This shift in population size is in part a result of interventions, such as antibiotics and vaccinations, which have successfully addressed communicable diseases that had been the leading cause of global mortality since the start of the 20th century.[27] Conversely, there has also been a global increase in public health behaviours that contribute to non-communicable disease such as smoking, poorer diet/nutrition, and a sedentary lifestyle.[28] As a result, global life expectancy has increased. For example, in the UK the number of people aged 65 years and above has increased from 9.2 million to over 11 million between 2011-2021.[29] This is in tandem with the prevalence of chronic conditions that have now become the leading cause of mortality across most of the developed world in the 21st century.[30]

Data reported by Wang[31] in 2016 suggest that 60% of global deaths between the period of 1980-2015 were the result of one of four major categories of chronic condition including cancer, cardiovascular disease (CVD), chronic lung conditions, and diabetes.[31] These conditions rarely present in isolation, with 1 in 3 adults worldwide reporting simultaneous diagnoses of more than one chronic condition, sometimes referred to as multimorbidity.[32,33] As of 2019, England had observed a 22% increase in the prevalence of multimorbidity since 2004 (30.8% *vs* 52.8%).[34] This prevalence rate appears to be higher than figures reported in

2015 from other European nations, such as Austria (28.3%), France (30.9%), and the Netherlands (16.2%).[35,36]

Based on pooled mean direct medical costs per capita, Tran *et al*[37] calculated an average annual cost of £650-122,025 per patient living with multimorbidity. Examples of multimorbidity-related costs include increased primary care and secondary care appointments, higher numbers of hospital admissions and poorer associated clinical outcomes such as length of stay and mortality, and unsurprisingly more complex and extensive prescriptions and/or treatment regimens to manage multiple diagnosed conditions.[38–40] Several risk-factors have been significantly associated with multimorbidity risk (Table 1.1) including disability, socio-economic deprivation, lower self-reported education, and an increased Body Mass Index (BMI).[34–36,41] However, gender (female) and increasing age are some of the most commonly identified predictors of multimorbidity. Of the two, age represents the highest proportional risk (79.6% of those >75 years of age reported multimorbidity)[36] and relative risk (RR) when adjusted by prevalence (those >80 years of age reported a multimorbidity prevalence 7.49 times higher than that of those aged 18-29).[34] For those over 65 years of age, the prevalence of multimorbidity rises dramatically to ~70%, however estimates as high as 98% have been reported.[42,43]

Table 1.1 – Factors Associated with Multimorbidity

Study	Factor	% Population (95% CI)	Prevalence Adjusted RR (95% CI)
Boersma *et al*[44]	Female	28.4 (27.5–29.4)	
	Increasing age (>65)	63.7 (62.3–65.1)	
	Public insurance	27.6 (25.5–29.9)	
	Living in rural areas	34.8 (32.8–37.0)	
Bezerra de Souza *et al*[35]	Female	34.8 (34.1–35.4)	
	Increasing age (≥80)	53.5 (52.2–54.7)	
	Low education level	40.2 (39.4–41.1)	
	Fair or poor self-rated health status	55.1 (54.2–55.9)	
	High self-reported loneliness	52.4 (50.4–54.5)	
	Low self-reported quality of life	44.0 (43.1–44.9)	
	BMI "Overweight"	30.5 (29.8–31.3)	
	BMI "Obese"	46.6 (45.4–47.8)	
	Reported a disability	66.1 (64.7–67.5)	
Head *et al*[34]	Female		1.18 (1·17–1·18)
	Deprivation (IMD 5)[a]		1.14 (1·12–1·15)
	Increasing age (≥80)		7.49 (7·38–7·60)
Van Oostrom *et al*[36]	Female	45.4	
	Increasing age (≥75)	79.6	

Notes: [a]IMD 5 refers to the UK IMD 2015 Scale, with a range of scores from 1 (least deprived) to 5 (most deprived). Countries included across the reported studies include: Austria, Belgium, Croatia, Czech Republic, Denmark, England, Estonia, France, Germany, Greece, Italy, Luxembourg, Netherlands, Poland, Portugal, Slovenia, Spain, Sweden, Switzerland

Abbreviations: IMD, Index of Multiple Deprivation; RR, Relative Risk; CI, Confidence Interval

1.2.1 Medications & Adherence in Chronic Disease

The coinciding increase in chronic disease prevalence and use of medicines is highlighted by the 2016 Health Survey Report[45] for England that indicated that from 2015-2016, 48% of adults had taken at least one prescription medicine and 24% had taken ≥3 medicines. Admittedly, the report did not restrict data collection to only individuals living with chronic conditions or multimorbidity, however it did identify a clear relationship between prescription medicines use and self-reported health. Of those participants reporting bad or very bad general health, 85% had used at least one prescribed medicine during the data collection period, compared to only 40% in those reporting good or very good general health.

The number of prescription items had also increased by 47% within the period of a decade (2006-2016) and equated to a cost of £9.2Bn for community prescriptions in 2016 alone. The total figure for spending on medicines (community and hospital-based prescriptions) in England was £20.9Bn, as reported by NHS Digital for 2019/20. This represents an increase of 9.9% from the previous year alone (£19Bn) and demonstrates the significant upward trajectory of national medicines use and expenditure. The use and reliance on medicines to treat patients, even those without chronic conditions, is evidently broad. Yet, their widespread use does not necessarily justify their efficacy in terms of cost nor patient outcomes. In fact, despite being the most widely used intervention in healthcare, there is a critical question to address – *are patients taking their medicines?*

Although, as stated previously, a figure of 50% is widely cited as the MA rate for patients living with chronic conditions, more recent estimates derived from studies spanning the last 10 years suggest a variable range of 30-75%, which is dependent on factors such as the clinical condition and type or complexity of the prescribed treatment regimen.[46–51] Consequences of non-adherence can include potential treatment failure, a higher risk of developing ADRs, increased likelihood of a hospital admission, prolonged length of hospital stays and an overall increased risk of mortality, particularly among older and multimorbid populations.[52–54] A 2018 UK observational study examining medication related harm, including ADRs, estimated an annual cost to the NHS of £396Mn, with approximately 25% solely attributed to non-adherence. Alternative estimates have suggested a figure closer to £930Mn in the UK, which was attributed to non-adherence in five chronic conditions alone including Type 2 Diabetes (T2D), chronic lung conditions (Chronic Obstructive Pulmonary Disease (COPD)/asthma), schizophrenia, hypertension, and hyperlipidaemia/Coronary Artery Disease (CAD).[55] In other parts of Europe and the US, annual costs associated with poor adherence are reportedly between £920Mn to £224Bn, respectively.[55] These large figures are

indicative of preventable costs that improvements in MA could look to address. Furthermore, MA has a critical role beyond cost avoidance alone in ensuring that each patient can derive the maximum benefit from their prescribed treatments while avoiding negative outcomes associated with non-adherence, particularly among individuals with a diagnosed chronic condition or multimorbidity. This sentiment echoes an earlier statement by the WHO and Haynes *et al*[56] in 2001 - "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."

Although the topics of chronic disease and multimorbidity are broad, there are two particular conditions that this thesis looks to address in relation to MA; T2D and COPD.

1.3 A Brief Introduction to Type 2 Diabetes

1.3.1 Definition of Type 2 Diabetes

Diabetes is the term for a wider set of metabolic conditions that is characterised by chronic hyperglycaemia (elevated blood glucose levels) related to the impaired regulatory function of the hormone, insulin.[57] Two major forms, Type 1 Diabetes (T1D) and T2D, account for most cases globally.[58] A T1D diagnosis indicates a complete lack or significant insufficiency of the pancreas to produce insulin, which is responsible for the regulation of glucose metabolism. Conversely, patients living with T2D are often able to produce insulin, however they have developed an insulin resistance over time that directly impairs the regulation of glucose metabolism leading to persistent hyperglycaemia.[58]

1.3.2 Prevalence of Type 2 Diabetes

Figures provided by the International Diabetes Federation (IDF) suggest a 5.3% increase in the global adult prevalence of diabetes from 4.7% in 1980 to 9.3% in 2019.[59] The incidence of T1D and T2D occur in a ratio of approximately 1:9, hence the vast majority of cases

reflect the latter diagnosis.[60] Other recent prevalence data were derived from the Global Burden of Disease (GBD) dataset (Institute of Health Metrics) by Khan *et al.*[61] The results of these data were inclusive of adolescents (>15 years of age) and indicated that 462Mn individuals were affected by T2D in 2017. The UK reported a prevalence of 8663 cases per 100,000, higher than the average prevalence rate for Europe (n=8529 per 100,000) and overall global prevalence (n=6059 per 100,000). Khan *et al*[61] highlight that while global prevalence is increasing at an alarming rate, particularly in less economically developed regions, the burden of disease, often referred to a Disability-Adjusted Life Years (DALYs) that is equivalent to the loss of one full year of health, was emerging most rapidly in Western Europe. Furthermore, forecast estimates were used to provide future projections for the global prevalence of T2D, which is expected to rise to 7079 cases per 100,000 by 2030 at the current trajectory.

1.3.3 Risk Factors for T2D

There are numerous risk factors associated with T2D with lifestyle factors being some of the most notable. A lack of physical activity, smoking, sedentary lifestyle, and excessive alcohol consumption are strong predictors of T2D risk, among several other chronic conditions e.g., Ischaemic Heart Disease (IHD).[62] In the 2012 report "Global physical activity levels: surveillance progress, pitfalls, and prospects", Hallal *et al*[63] identify that the global proportion of physically inactive adults (>15 years of age) is 31.1% (95% Confidence Interval (CI) 30.9, 31.2) of the population based on data available for 122 countries included in the study. Lifestyle factors, such as the significant shift in global physical activity, are inherently linked and contribute to obesity, which has been demonstrated as the most significant epidemiological predictor of T2D irrespective of any links to potential genetic factors.[64] In fact, a recent case-cohort study conducted by Schnurr *et al*[62] (n=9556) examined the incidence of T2D among patients stratified within groups according to obesity, genetic

predisposition (defined as the Genetic Risk Score (GRS)), and those with an 'unfavourable lifestyle'. The effects of a high GRS (Hazard Ratio (HR) 2.00, 95% CI 1.76, 2.27) or unfavourable lifestyle on T2D risk were found to be modest (HR 1.18, 95% CI 1.06, 1.30). Conversely, the effect of obesity on T2D risk (HR 5.81, 95% CI 5.16, 6.55) was high. The study also identified that even among participants with a low GRS and favourable lifestyle, obesity was associated with a >8-fold risk of T2D when compared to normal-weight study participants with comparable GRS and lifestyles. Further evidence of the interaction between lifestyle and genetics is provided by Yu *et al*[65] in their prospective evaluation (n=2546) of alcohol consumption and genetic predisposition on T2D prevalence. The most dramatic association between alcohol and T2D risk was identified among participants with the lowest GRS who were >3 times more likely to experience glucose deterioration when compared with non-drinkers (OR 3.33; 95% CI 2.04, 5.43). Similarly to Schnurr *et al,*[62] the results suggest that modifiable lifestyle behaviours related to obesity, such as alcohol consumption or physical activity, have a critical role to play as predictors of T2D risk. Interestingly, even genetic, or familial predisposition to T2D may be partially mediated by obesity. Evidence for this link is provided by Dabalea *et al*[66] who identified that siblings exposed to intrauterine T2D were almost four times as likely to develop the condition than their siblings without in utero exposure (OR 3.7, p=0.02). More specifically, in utero exposure was associated with an increase in BMI by 2.6 kg/m^2 when compared to offspring from pregnancies of mothers without T2D.

1.3.4 Symptoms & Complications of T2D

Given the progressive nature of T2D, a large proportion of patients remain asymptomatic in the early stages of the disease.[67] A decreased sensitivity to the hormone insulin leads to impaired glucose metabolism causing hyperglycaemia or 'high blood sugar'.[68] Overtime, hyperglycaemic episodes become increasingly severe leading to symptoms such as frequent

urination (polyuria), thirst (polydypsia), and hunger (polyphagia). Fatigue and blurry vision are also common. Prolonged hyperglycaemia is also associated with more frequent infections (particularly genital, urinary, oral, and dermatological conditions) and delayed wound healing. The severity and type of symptoms experienced by people living with T2D are significantly correlated with socio-clinical and disease-related characteristics.[69] For example, Bulpitt *et al*[69] identified that the likelihood of reporting a complaint related to T2D symptoms was more significant in those with a higher BMI or Fasting Plasma Glucose (FPG) as a measure of hyperglycaemia ($p<0.05$).

T2D complications are often classified by their effects on either small (microvascular) or large (macrovascular) blood vessels. Microvascular complications are associated with retinal damage and reduced vision (retinopathy), impaired kidney function (nephropathy), and nerve damage (neuropathy) that may lead to tingling, loss of sensation or possibly autonomic changes such as urinary symptoms and sexual dysfunction.[70] Excluding the duration of a T2D diagnosis, poor glycaemic control, hypertension (high blood pressure), and hyperlipidaemia (high cholesterol/serum lipids) are also confounding risk factors associated with the development of microvascular complications. A 2020 review by Faselis *et al*[70] estimates that 1 in 4 people with T2D are affected by nephropathy and retinopathy, while approximately 50% will experience symptoms of neuropathy.

Macrovascular complications comprise CAD, cerebrovascular disease (affects cerebral circulation and includes conditions such as stroke, transient ischaemic attack, and aneurysms), cardiomyopathy (damage to cardiovascular muscle tissue), arrythmias, peripheral artery disease, and sudden death.[71] Similarly to microvascular complications, obesity, hypertension, and hyperlipidemia are all strong predictors of macrovascular complications. These complications are of particular concern given that CVD is the leading

cause of mortality for patients living with T2D as well as being responsible for some of the largest health economic costs.[72,73]

1.3.5 Diagnosis & Management of T2D

1.3.5.1 Clinical Features of T2D

The diagnosis of T2D involves a comprehensive assessment of related clinical features including symptoms, risk factors, and a measure of persistent hyperglycaemia (Table 1.2).[74] HbA_{1c} (haemoglobin $A1_c$), a measure of glycosylated haemoglobin over the previous 2-3 months period, is a significant clinical biomarker for both the diagnosis and monitoring of T2D with significant correlations to T2D related complications.[75] Similarly to HbA_{1c}, FPG is a reliable diagnostic measure when evaluated in the presence of symptoms associated with hyperglycaemia. However, it should be noted that repeated measures are recommended as part of the national guidance for the diagnosis of T2D in adults.[74]

Table 1.2 – Diagnostic Clinical Features for T2D in Adults

Clinical Features of T2D	
Symptoms[a]	• Polydipsia • Polyuria • Blurred vision • Unexplained weight loss • Recurrent infections • Fatigue • Polyphagia
Risk Factors[a]	• Obesity • Family history • Asian, African, and Afro-Caribbean ethnicity • Gestational diabetes and intrauterine exposure • Diet • Sedentary lifestyle
Measures of Hyperglycaemia	• HbA_{1c} ≥48mmol/mol (6.5%)[b] • FPG ≥7.0 mmol/L • Random plasma glucose ≥11.1 mmol/L in the presence of symptoms

Notes:[a]Non-exhaustive list of common examples for symptoms and risk factors; [b]Although more commonly reported as mmol/mol, equivalent % values for HbA_{1c} are also reported.

Abbreviations: HbA_{1c}; haemoglobin $A1_c$;FPG, fasting plasma glucose

It is critical that clinicians and high-risk groups of individuals have an awareness of T2D clinical features given that as many as 25% of people diagnosed with T2D will present with microvascular disease.[76] Furthermore, early recognition and diagnosis of T2D has a significant impact on longitudinal clinical outcomes. In a meta-analysis of 26 observational studies (n=1,325,493), a 1-year increase in age at diagnosis (inferring later onset of T2D) was associated with a 4%, 3% and 5% decreased risk of all-cause mortality, macrovascular disease, and microvascular disease, respectively.[77] Hence, early onset of disease requires effective treatment to reduce the risk of long-term complications, including mortality. Lifestyle interventions, such as diet, exercise, and weight loss in conjunction with pharmacological agents have an important role to play as part of a stepwise approach to intensification of blood glucose management.[78] Again, HbA_{1c} is an important clinical biomarker as a target for treatment maintenance or intensification (Table 1.3). In addition, socio-demographic features, duration of T2D, risk of adverse effects, and comorbidities such as CVD and renal disease need to be taken into consideration. Treatment targets should be individualised to each patient, however they usually range from ≤48mmol/mol - ≤53mmol/mol depending on the type of treatment. Intensification to dual or triple drug therapy is often triggered in patients with inadequately controlled hyperglycaemia (≥58 mmol/mol (7.5%)). Measurement of HbA_{1c} is recommended at 3-monthy intervals upon treatment initiation, then moving to 6-monthly monitoring when the HbA_{1c} is stable and treatment choice maintained. HbA_{1c} data provide a valuable insight into the glycaemic control of individuals living with T2D over the previous 2-3 months, which may be indicative of adherence to lifestyle measures and medicines as part of a treatment regimen.[75] HbA_{1c} is also a useful prognostic measure. In a pooled analysis of studies (n=10) that evaluated the relationship between HbA_{1c} and CVD (specifically coronary heart disease and stroke), a 1% increase in HbA_{1c} (equivalent to 10mmol/mol) was associated with a higher risk of

developing macrovascular disease (n=7435, RR 1.18, 95% CI 1.10, 1.26).[79] Moreover, Monami *et al*[80] conducted a logistic regression analysis with individuals reporting a baseline HbA_{1c} of 6.5-7.4% (48-57.4mmol/mol) as the reference group. The results demonstrated an increased RR of mortality by 1.86 (95% CI 1.16, 2.99) and 2.56 (95% CI 1.64, 4.01) in individuals reporting HbA_{1c} baseline values of 7.5-8.4% (58-68.3mmol/mol) and >8.4% (>68.3mmol/mol), respectively.

Table 1.3 – Treatment Targets for T2D

Treatment Regimen[78]	HbA_{1c} Target
Lifestyle advice including diet management	≤48 mmol/mol (6.5%)
Lifestyle including diet combined with a single drug not associated with hypoglycaemia (such as metformin)	≤48 mmol/mol (6.5%)
Drug treatment associated with hypoglycaemia (such as a sulfonylurea)	≤53 mmol/mol (7.0%)
Two or more drug treatments (Dual/Triple Therapy)	≤53 mmol/mol (7.0%)

1.3.5.2 Stepwise Management of T2D

There are various pharmacological agents available for the management of T2D (Table 1.4).[78,81] Metformin is an example of a biguanide and is the most common first-line agent for the treatment of T2D. Metformin has positive effects on HbA_{1c} reduction (10-20mmol/mol or 1-2%), lipid metabolism, and attenuation of hypertension without the risk of hypoglycaemia, which is more frequently associated with sulphonylureas and meglitinides.[82,83] With metformin, as in most cases of treatment initiation, doses of this as a single agent should be uptitrated to achieve a balance of the most positive clinical outcome in tandem with the least adverse reactions or side-effects. However, initiation of dual therapy with Sodium-Glucose Type 2 Receptor (SGLT2) inhibitors should be considered as soon as tolerability of metformin is confirmed in patients that have chronic heart failure (CHF), established

atherosclerotic CVD, or are at high risk of developing CVD. The results of two recent large-scale trials of SGLT2 inhibitors in individuals with Heart Failure with reduced Ejection Fraction (HFrEF), DAPA-HF[84] (dapagliflozin therapy) and EMPEROR-Reduced[85] (empagliflozin therapy), have prompted an update to the T2D management guidelines within the last few years. A meta-analysis of patient (n=8474) outcomes across both trials demonstrated a 13% pooled reduction in all-cause mortality (HR 0.87, 95% CI 0.77, 0.98; *p*=0·018), 14% pooled reduction in cardiovascular death (HR 0.86, 95% CI 0.76, 0.98; *p*=0·027), and 38% pooled reduction in renal endpoints (<50% decrease in renal function, end stage renal disease, or renal death) (HR 0.62, 95% CI 0.43 ,0.90; *p*=0·013).[86] The early initiation of SGLT2 inhibitors therefore prevents macro- and microvascular disease, as well as reducing the risk of mortality in T2D where both cardiovascular and renal comorbidity are common. For those without established CHF, CVD, or at high-risk of developing CVD, dual therapy with metformin and a sulphonylurea, Dipetidylpeptidase-4 (DPP-4) inhibitor, or pioglitazone should be considered. Only after dual therapy fails to adequately control hyperglycaemia should triple therapy with a combination of the mentioned agents be considered, this may also include the introduction of insulin as part of the treatment regimen. Where this approach is found to be ineffective, a Glucagon-like-peptide-1 (GLP-1) receptor agonist such as dulaglutide may be considered, particularly in obese patients where a significant reduction in both BMI and HbA_{1c} is needed.[87]

Table 1.4 – Pharmacological Agents for T2D Management

Class	Example Agents	Mechanism of Action	Contraindications/Cautions
Biguanides	Metformin	Inhibition of gluconeogenesis	Lactic acidosis Acute/chronic renal impairment
Sulphonylureas	Gliclazide, Glimepiride, Glipizide,	Stimulation of pancreatic β cells to produce insulin	Risk of hypoglycaemia exacerbation Exacerbation of weight gain
α-glucosidase Inhibitor	Acarbose	Delays digestion of absorption of starch and sucrose	Inflammatory Bowel Disease (IBD) Hernia
Meglitinides	Repaglinide	Stimulation of pancreatic β cells to produce insulin	Ketoacidosis Risk of hypoglycaemia
Thiazolidinediones	Pioglitazone	Increased insulin sensitivity (upregulation of glucose utilisation)	Previous/Active bladder cancer History of heart failure
Dipetidylpeptidase-4 (DPP-4) Inhibitors	Alogliptin, Linagliptin, Sitagliptin	Upregulate incretins for increased insulin secretion	History of pancreatitis
Glucagon-like Peptide 1 (GLP-1) Receptor Agonists	Dulaglutide, Exenatide, Semaglutide	Increased insulin secretion	History of severe gastrointestinal disease
Sodium-glucose Co-transporter 2 (SGLT2) Inhibitors	Canagliflozin, Dapagliflozin, Empagliflozin	Inhibition of renal glucose reabsorption	Hypotension Ketoacidosis
Insulin	Rapid acting Short acting Soluble insulin Intermediate acting Long acting	Increased glucose utilisation	Risk of hypoglycaemia

1.4 A Brief Introduction to Chronic Obstructive Pulmonary Disease (COPD)

1.4.1 Definition of COPD

COPD is an umbrella term used to describe respiratory conditions that are characterised by a progressive and irreversible decline in lung function. Changes in lung function may restrict airflow as a result of an abnormal inflammatory response to noxious particulate matter or gases.[88]

1.4.2 Prevalence of COPD

A 2019 systematic review (SR) conducted by Blanco *et al*[89] identified a global COPD prevalence of 13.1% (95% CI 10.2, 15.6). Data were derived from literature produced between 1995-2019 and provided relevant prevalence information from 5 major geographical regions including Africa, Europe, Asia, Oceania, and the Americas. Comparatively, similar systematically reviewed epidemiological data reported in 2010 provided a global prevalence rate of 11.7% (95% CI 8.4, 15.0), hence there has been a significant increase in the number of COPD diagnoses globally within the last decade. Given both the rising prevalence as well as the progressive and irreversible nature of the condition, COPD is associated with a large mortality burden and as such is the fourth leading cause of death worldwide.[90] Approximately 3Mn people die each year as a direct result of COPD. This figure is expected to reach 4.5Mn by 2030, which would make COPD the third leading cause of death globally based on current predictive models of disease-related mortality.[91]

COPD is commonly diagnosed in tandem with other conditions, such as CVD, osteoporosis, metabolic syndrome, and mental health diagnoses such as anxiety and depression.[92] This complex picture of multimorbidity contributes to COPD being ranked the 11th most burdensome condition globally among working-age patients.[93] In 2017, the WHO estimated

the worldwide net loss of productivity associated with COPD to be 27,700 DALYs; this represents a global increase in DALYs of 26% within the last 3 decades.[91]

1.4.3 Risk Factors for COPD

The disproportionately high prevalence of COPD among ageing populations and those exposed to tobacco smoke and other airborne pollutants provides evidence for their role as significant risk factors for the condition.[94] Although individual susceptibility for the effects of tobacco smoke vary widely depending on age, sex assigned at birth, and genetic predisposition to smoking-related morbidity, roughly 50% of heavy smokers will go on to develop COPD.[95] Understanding the genetic predisposition for COPD is somewhat more complex given that widespread exposure to airborne pollutants makes it challenging to delineate between purely environmental *vs* hereditary risks. Despite this, one specific example of genetic influence is found with the familial deficiency of alpha-1 antitrypsin (AATD), which has been associated with a greater prevalence of COPD in certain Northern and Eastern European populations (Incidence Ratio (IR) 0.12% 95% CI 0.08, 0.24).[95,96] Historically, COPD has been regarded as a disease that affects older men. However, a recent meta-analysis of 194 eligible studies reporting on gender-specific COPD prevalence, conducted by Ntritsos *et al*,[97] identified a summary prevalence of 9.23% (95% Credible Interval (CrI); 8.16, 10.36) in men and 6.16% (95% CrI 5.41, 6.95) in women. These epidemiological data highlight a clinically relevant prevalence of COPD among women. Furthermore, similarly reported epidemiological data from 12 countries across Asia, the Americas, and Europe for adults >40 years of age (n=4343) indicate a more equal COPD prevalence rate between men (range=6-14%) and women (5-11%).[98] The differences noted in the literature have been attributed to the greater prevalence of smoking among men, hence mechanisms of risk may be more related to behavioural factors rather than any specific inherent gender-based bias.[98]

Early-onset of COPD is often defined as those with a diagnosis before 50-55 years of age.[98,99] This definition is indicative of the fact that COPD affects predominantly older populations. Yet, it is interesting to note the substantial impact of intrauterine, childhood, and adolescent lung growth and development as a predictor of COPD risk. The Forced Expiratory Volume in 1 Second (FEV_1) is used as a lung function test in a range of respiratory conditions. In a pooled analysis of birth weight and FEV_1 in adults, Lawlor *et al*[100] identified a moderately positive and linear relationship, with each 1kg increase in birth weight associated with a 0.048 (95% CI 0.026, 0.070) change in FEV_1. Hence, a higher birth weight improves FEV_1 outcomes. Poor lung growth throughout gestational, childhood, and adolescent developmental phases is indicative of low FEV_1 in early adulthood, a strong predictor of both COPD risk, as well as all-cause mortality.[101,102] This association provides further insight into the interconnected nature of COPD and exposures to behavioural or environmental factors that increase risk. A longitudinal analysis (n=579,466) of individuals living with COPD compared groups with either a low or high socio-economic status and reported a prevalence of 32.1% *vs* 23.0%, respectively.[103] Poverty is a strong predictor of airflow limitation, smoking, and low birth weight, which may in part provide evidence for this stark discrepancy in prevalence of COPD in socio-economically deprived populations.[104,105]

1.4.4 Symptoms & Complications of COPD

In a cross-sectional study of European adults living with COPD, 92.5% (n=2258/2411) of individuals reported experiencing COPD symptoms in the 7-day period prior to their participation.[106] Breathlessness was the most common symptom (72.5%). Other frequent symptoms include phlegm, cough, wheezing, and chest tightness.[107] Although breathlessness is the hallmark symptom associated with COPD, Miravittles and Ribera[108] provide clarification on the misconception that the progression of COPD follows a linear pattern of declining lung function and symptom invariability; in fact, quite the opposite is true. In a

cohort of 289 patients with severe COPD, 46% reported that the morning period was when they experience their worst symptoms.[109] Moreover, almost two thirds (62.7%, n=3832/6112) of individuals report daily or weekly changes to their symptoms, accompanied by a significant increase in COPD symptom exacerbations in winter compared to summer climates (RR 0.8, 95% CI 0.7, 0.9; $p<0.001$). It is therefore important to recognise that while patients with advanced COPD will experience more severe symptoms compared to those with mild disease, the vast majority will experience daily, weekly, and even seasonal changes to their symptoms.[107,110]

Not only are symptoms experienced by people living with COPD strong predictors of Health-Related Quality of Life (HRQoL), but they also provide relevant prognostic data. For example, in a meta-analysis (n=2510) of COPD HRQoL and wellbeing, dyspnoea was found to be most strongly correlated (Pearson weighted correlations = r) factor with health status (r=0.507, 95% CI 0.371, 0.622).[111] Moreover, night-time COPD symptoms are significantly associated with future COPD exacerbations (HR 2.3, 95% CI 1.7, 3.0), hospital admission (HR 3.2, 95% CI 2.3, 4.4) and mortality (HR 1.7, 95% CI 1.2, 2.3).[112] There is also a critical relationship between COPD and related complications that predict a heavy HRQoL, morbidity, and mortality burden. People living with COPD have demonstrated a four-fold increase in risk for developing lung cancer, specifically squamous cell cancers.[113] Pulmonary hypertension is another common complication of COPD that results in decreased survival (33% *vs* 66%, $p<0.001$, 5-year survival for COPD with and without pulmonary hypertension respectively).[114] Furthermore, COPD is associated with a systemic inflammatory response that has demonstrated a significant increase in insulin-resistance when compared to healthy individuals (p=0.032) that is likely to contribute to the disproportionate risk of developing metabolic syndrome, including both CVD and T2D, in patients living with COPD.[115] Cachexia (muscle wasting),[116] psychological comorbidities (anxiety and depression),[117] and

chest infections are also highly prevalent among people living with COPD.[118] Although more nascent, early evidence has also suggested that there is a significant interaction between COPD and Covid-19.[119–121] A pooled analysis of Covid-19 clinical studies (n=59) between November 2019 and Jan 2021 identified that a COPD diagnosis was associated with a >4 times increased odds of hospitalisation (Odds Ratio (OR) 4.23, 95% CI 3.65,4.90) for patients with Covid-19.[122]

1.4.5 Diagnosis & Management of COPD

1.4.5.1 Clinical Features of COPD

A reliable COPD diagnosis requires a combination of symptoms, risk factors/relevant history, and evidence of irreversible airflow obstruction using spirometry measures, such as the FEV_1/Full Vital Capacity (FVC) ratio (Table 1.5).[123]

Table 1.5 - Diagnostic Clinical Features for COPD in Adults

Clinical Features of COPD	
Symptoms[a]	• Exertional breathlessness • Chronic cough • Regular sputum production • Frequent winter 'bronchitis' • Wheeze
Risk Factors[a]	• Current or ex-smoker • Occupational or environmental exposure to hazardous particulates/gases • Family history of COPD • Low gestational weight • Recurrent childhood respiratory infections
Spirometry[b]	• FEV_1/FVC <0.7 • FEV_1/FVC 0.6 – 0.8 – Repeat spirometry is recommended

Notes:[a]Non-exhaustive list of common examples for symptoms and risk factors; [b]Spirometric values should be calculated using a spirometer after administration of a short-acting bronchodilator to provide a reliable measure of irreversible airway obstruction

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, full vital capacity

There are several spirometry values that are used as part of diagnostic and prognostic criteria for COPD and other obstructive and restrictive respiratory conditions (Table 1.6). Abnormal

spirometry values in the absence of symptoms or risk factors should not be used to inform a clinical diagnosis of COPD, however they may in fact be indicative of an alternative pathology that requires further investigation.[123]

Table 1.6 – Definitions of Lung Function Tests in COPD

Lung Function Test/Spirometry	Definition
Forced Expiratory Volume in 1 Second (FEV_1)	Volume of air that can forcibly be exhaled in one second, after full inspiration
Percentage Predicted FEV_1 (FEV_1 % Pred)	FEV_1 of the patient divided by the average FEV_1 in the population for any person of similar sex, age and body composition
Full Vital Capacity (FVC)	Volume of air that can forcibly be exhaled after full inspiration
FEV_1/FVC	Proportion of a person's vital capacity that they are able to expire in the first second of forced expiration (FEV_1) to the full, forced vital capacity (FVC)

Spirometry may also be used to classify COPD in terms of airflow obstruction with several frameworks using either FEV_1 Predicted or FEV_1/FVC ratio (Table 1.7). These frameworks include the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[124] and National Institute for Health and Care Excellence (NICE)[125] guidelines that provide an indication of disease severity from Stage 1 (mild) to Stage 4 (very severe).

Table 1.7 – Classification of Severity of Airflow Obstruction

Post-bronchodilator FEV1/FVC	FEV1 % predicted	GOLD (2008)	NICE (2010)
<0.7	≥80%	Stage 1 – Mild	Stage 1 – Mild
<0.7	50–79%	Stage 2 – Moderate	Stage 2 – Moderate
<0.7	30–49%	Stage 3 – Severe	Stage 3 – Severe
<0.7	<30%	Stage 4 – Very Severe (or FEV1 below 50% with respiratory failure)	Stage 4 – Very Severe (or FEV1 below 50% with respiratory failure)

The GOLD report, widely seen as a global gold-standard for the diagnosis and management of COPD, recommends an assessment of symptom severity in tandem with spirometry to help identify the most appropriate choice of pharmacological treatment.[124] The modified Medical Research Council (mMRC)[126] breathlessness/dyspnoea scale and COPD Assessment Test (CAT)[127] are two of the most frequently used measures of symptom severity and impact on daily activities. Both are short and simple examples of self-administered measures of a patient's experience or clinical outcomes, often referred to as Patient-Reported Experience or Patient-Reported Outcome Measures (PREMs/PROMs). The mMRC comprises five items that explore breathlessness during daily activities that provide a grading between 0 (almost no impact) to 4 (complete incapacity), with scores ≥2 usually delineating between individuals as either less or more breathless. A worseninig mMRC grade has previously been associated with a decrease in FEV_1% Pred, higher rates of COPD exacerbations, obesity, and both psychological and cardiovascular comorbidities such as depression and heart failure, respectively.[128] The CAT comprises eight items on a 0-5 Likert scale response system for a total score out of 40 that assesses symptoms such as cough, phlegm, chest tightness and sleep as a few examples. Scores of 0–10, 11–20, 21–30, 31–40 represent low, medium, high, or very high impact, respectively. Similarly to mMRC, CAT scores are predictive of both

exacerbations and symptoms of depression, however they have also been associated with health status deterioration and increasing risk of mortality.[129]

1.4.5.2 Stepwise Management of COPD

A combination of assessments, referred to as the ABE assessment, is used to inform the most appropriate pharmacological treatment regimen based on a spirometry, FEV_1% predicted value, a history of exacerbations and an mMRC or CAT score to provide a classification from A, B or E based on symptoms (Table 1.8).[124] The ABE assessment usually reflects a best-practice approach to a treatment decision at diagnosis, whereas factors such as dyspnea and/or the number and consequence of exacerbations (e.g., leading to a hospital admission) usually inform follow-up pharmacological management.[125]

Table 1.8 – Adapted ABE Assessment for Exacerbations & GOLD Category[124]

	Symptoms	
	mMRC 0-1 CAT <10	mMRC ≥2 CAT ≥10
Exacerbations	GOLD Category	
0 or 1 not leading to a hospital admission	A	B
≥2 or ≥1 leading to a hospital admission	E	

Irrespective of the results from the initial ABE assessments, several core non-pharmacological treatment recommendations apply to any individual diagnosed with COPD as outlined in the NICE COPD guidance for over 16s,[123] including:

- Smoking cessation.
- Provision of pneumococcal and influenza vaccines (although not consistently described across all guidance, Covid-19 vaccinations should also be recommended).

- Co-development of a personalised self-management plan.
- Optimisation of treatment for other comorbidities.
- Where applicable, pulmonary rehabilitation should also be offered.

Only if the above criteria have been met is it recommended to initiate pharmacological therapy (Table 1.9).

Table 1.9 – Pharmacological Agents for COPD Management

Class	Example Agents	Mechanism of Action	Contraindications/Cautions
Short-Acting Beta$_2$ Agonist (SABA)	Salbutamol, Terbutaline	Short-acting airway smooth muscle relaxation *via* β_2 adrenergic receptor	Hypokalaemia Arrhythmias
Long-Acting Beta$_2$ Agonist (LABA)	Formoterol, Indacaterol, Salmeterol	Long-acting airway smooth muscle relaxation *via* β_2 adrenergic receptor	Hypokalaemia Arrhythmias
Short-Acting Muscarinic Antagonist (SAMA)	Ipratropium	Promotion of anticholinergic relaxation of muscle tissue and reduced mucus secretion (Short-acting)	Cystic Fibrosis Bladder Obstruction Glaucoma
Long-Acting Muscarinic Antagonist (LAMA)	Tiotropium, Glycopyrronium, Aclidinium, Umeclidinium	Promotion of anticholinergic relaxation of muscle tissue and reduced mucus secretion (Long-acting)	Cystic Fibrosis Bladder Obstruction Glaucoma Prostatic Hyperplasia
Inhaled Corticosteroid (ICS)[a]	Fluticasone, Beclometasone, Budesonide	Inhibition of inflammatory cells (e.g., eosinophils) and promotion of airway smooth muscle relaxation	Type 2 Diabetes Osteoporosis
Macrolides[b]	Azithromycin	Inhibits bacterial protein synthesis (antibiotic)	QT-Interval Prolongation
Phosphodiesterase Type-4 Inhibitor (PDE4I)	Roflumilast	Decreases inflammatory mechanism *via* regulation of cyclic AMP activity	Immunosuppressive Therapy History of Cardiac Failure
Xanthines	Theophylline	PDE3/4 inhibition leading to bronchodilation	Arrhythmias Hypokalaemia

Notes:[a]ICS therapy is provided as part of a dual combination inhaled therapy with LABAs, or triple combination inhaled therapy with LABAs + LAMAs e.g, Trelegy Ellipta® (Fluticasone (ICS), Umeclidinium (LAMA), Vilanterol (LABA)); [b]Macrolides are a class of antibiotic, specifically azithromycin may be prescribed under specialist use as a prophylactic agent for individuals with recurrent respiratory infections/exacerbations whereby the benefits of prolonged antibiotic outweigh risks.

Using the ABE assessment results, a stepwise approach to the selection of treatment at diagnosis can be made based on the GOLD classification[124] from A, B or E:

A. Short-acting bronchodilator (Inhaled)
B. Long-acting bronchodilator and a long-acting antimuscarinic (LABA and LAMA) (Combination inhalers may be more suitable and effective than single devices and should therefore be considered)
E. LABA + LAMA (Combination inhalers to be considered) + an Inhaled Corticosteroid (ICS) if eosinophils >300

When making a decision at any stage of treatment, which may include at diagnosis, as part of maintenance therapy, or in response to an exacerbation, it is always recommended that healthcare professionals (HCPs) review an individual's inhaler technique. Primary endpoints include the alleviation of bronchoconstriction and mucus secretion, hence short-acting bronchodilators (referred to as SABAs) or short-acting anti-muscarinic agents (referred to as SAMAs) are often prescribed as first-line therapy. Treatment intensification e.g., moving to a combination (dual (LABA/LAMA) or triple (LABA/LAMA/ICS)) inhaled therapy may be considered in those experiencing persistent dyspnea or frequent exacerbations. Roflumilast may be considered after triple inhaled therapy (ICS + LABA + LAMA) in those with chronic bronchitis and FEV_1 <50%. Similarly, prophylactic azithromycin may be considered in former smokers with persistent exacerbations on triple therapy. Individuals with advanced disease, treatment resistance, or limitations/incapacity to tolerate inhaled medicines may be considered for treatment with oral corticosteroids, theophylline, and/or long-term oxygen therapy (LTOT).[123]

1.5 A Review of Medication Adherence Determinants, Models, and Measures

1.5.1 The 'Process' of Adhering to Medicines

Despite the availability of clear diagnostic, classification, and prescribing guidance for conditions such as COPD and T2D, the use of these data to inform the initiation of pharmacological therapy reflects only one part of the patient-prescriber journey with medicines, particularly in relation to MA. A 2012 SR of adherence literature published over the previous four decades was conducted by Vrijens *et al*[130] with a view "to propose a new taxonomy, in which adherence to medications is conceptualised, based on behavioural and pharmacological science, and which will support quantifiable parameters." This work rationalised adherence terminology across a total of 146 papers to provide a new conceptual foundation of adherence-related taxonomy comprising three elements:[130]

1. Adherence to medications – the process by which patients take their medicines, which includes three core components:
    a. Initiation – patient takes the first dose of medication.
    b. Implementation – the extent to which the patient's medication taking behaviour corresponds with the prescribed regimen, from initiation until the final dose of medication is taken.
    c. Discontinuation – the end of treatment whereby a medication is omitted, and no subsequent medications are taken.
        i. Persistence – sits across the three core elements and reflects the time between initiation and the final dose of medication being taken that immediately precedes discontinuation.
2. Management of adherence – Processes for monitoring and supporting MA, which may be by health systems, prescribers, and social networks.
3. Adherence-related sciences – Disciplines that look to address causes/consequences related to prescribed *vs* actual medicines exposure (adherence)

1.5.2 Drivers of Medication Adherence Behaviour

Contextualising the process by which medicines are prescribed, taken, and discontinued facilitates a wider discussion on the complex interplay of determinants that drive and contribute to MA-related behaviour. For example, individuals may delay or avoid initiation of medicines due to concerns related to side effects, limitations to their awareness of the disease and the intended positive outcomes associated with treatment, or even as a result of an emotional reaction to a novel diagnosis that may also be influenced by their health literacy or cultural perceptions of medicines and disease.[131–133] Interestingly, these findings even extend to more imminently life-threatening conditions such as cancer. Multivariate modelling was used to assess the association between factors related to non-initiation of adjuvant hormonal therapy in patients (n=725) with non-metastatic hormone receptor (HR)-positive breast cancer.[134] Despite adjuvant hormonal therapy decreasing breast cancer recurrence and increasing overall survival rates, 28.8% (n=209) of patients did not initiate their treatment, which was predominantly associated with negative beliefs about treatment efficacy (OR 1.42, 95 % CI 1.18, 1.70). Conversely, non-initiation was less likely in patients who reported high patient-physician communication (OR 0.96, 95% CI 0.93, 0.99) and in those with positive beliefs about treatment efficacy (OR 0.40, 95% CI 0.34, 0.62).

Similarly, poor perceptions of treatment efficacy also increase the likelihood of pharmacological therapy discontinuation, particularly where no immediate or visible benefit may be observed by the patient e.g., antidepressant therapy whereby the perception of any positive change can take 6-8 weeks from initiation of treatment.[135] Furthermore, patients that report a higher number of prescribed medicines (increasing treatment regimen complexity), psychological or other significant comorbidities (e.g., cancer), lower levels of self-reported education, development of an ADR, and higher healthcare utilisation are also more likely to discontinue their treatment; these findings have been reported across a wide range of

pathologies from Human Immunodeficiency Virus (HIV) to osteoporosis.[136–140] In a longitudinal cohort study of patients (n=1521) prescribed a triple regimen of medicines (beta-blocker, aspirin and a statin) as part of a pharmacological preventative strategy following a myocardial infarction, just over one-third (33.67%, n=512) discontinued ≥1 of their treatments.[140] Those patients that completely discontinued their medicines after 1 month had a significantly lower 1-year survival rate than those who continued ≥1 medicine as part of the regimen (88.5% *vs* 97.7%; $p<0.001$). It is evident that discontinuation persists in populations whereby such behaviour is associated with clear immediate risks, hence highlighting that the perceived efficacy of treatments may not be enough to tackle poor MA even among the highest-risk groups of patients.

Although far from exhaustive, the discussion above does provide an insight into MA-related factors and their links to broader groups of behavioural determinants (factors that influence an individual's decision to adopt or change a particular behaviour) such as:

- Sociodemographics e.g., level of education.
- Beliefs about medicines/disease e.g., perceived harm or perceived limitation to potential benefits of treatment as well as the severity of disease
- Patient experience e.g., development of an ADR or side effects.
- Health status e.g., the number of comorbidities and prescribed medicines, or utilisation of healthcare services.
- Identity e.g., cultural impact on health literacy or perceptions of medicines
- Relationships e.g., good communication between patients and prescribers

It is critical to note that these factors or behavioural determinants do not exist in isolation, rather patients' behaviours when taking medicines are often the result of multiple evolving

interactions across these factors and determinants making MA "extremely complex and individual" to each patient.[141]

1.5.3 Theoretical Models of Behaviour

Several theoretical models of behaviour (TMB) have been used to describe and understand MA and the interplay between drivers of MA-related actions, or in some instances inaction (Table 1.10). Although each model provides some distinct view on the drivers of MA which are complex and individual to each patient, some common themes exist. Rosenstock's[142] Health Belief Model (HBM) describes patients' attitudes towards medicines in the context of risk against value, such that a high perception of risk associated with the consequences of disease, such as complications, are likely to motivate MA-related behaviour. Similarly, Protection Motivation Theory (PMT)[143] explores the potential vulnerability to negative consequences as a 'perceived threat' that has a direct influence on an individual's motivation to protect themselves from harm, which may take the form of adhering to a particular treatment regimen. In a sense, both models articulate an individual's motivation through the lens of risks *vs* benefits associated with taking medicines. However, whereas the HBM and PMT centre individual perceptions of harm *vs* benefit at the core of behaviour change, the Social Cognitive Theory (SCT)[144] and the Theory of Planned Behaviour (TPB)[145] introduce a wider array of environmental and social factors. In this context, attitudes towards MA may be shaped by the experiences of social groups around the individual – this may also be influenced through a broader cultural context (social norms) e.g., cultural preferences for herbal/traditional medicines have demonstrated reduced adherence to prescribed treatments in several populations.[146] Interestingly, the most pervasive construct (a label for a domain of related behaviours) across all four cited TMB is self-efficacy, which can be described as an individual's confidence in their ability to successfully take an action.

Table 1.10 – Summary of TMB in relation to MA

Model	Context and Application to MA
HBM[142]	• Patients' attitudes toward their health status affect the way they take their medicines. • Perceived severity of disease and perceived susceptibility to the consequences of that disease inform the overall perceived threat – if perceived threat is high, individuals are more likely to engage in a particular behaviour that reduces risk. • Proposed behaviour change is also assessed through the lens of perceived benefits e.g., positive outcomes associated with taking a medicine, and perceived behaviours that may make a change in behaviour difficult – combined these reflect the perceived value – if the perceived value of a change in behaviour is low, this may prevent engagement. • Example: Perceived susceptibility to disease-related complications was significantly (p=0.017) associated with higher levels of medication adherence in a cohort of hypertensive Chinese patients (n=232)[147]
PMT[143]	• PMT comprises perceived risk, motivation to protect oneself, and engagement with recommended health behaviours. • Perceived vulnerability/susceptibility to a health threat and the perceived severity of the consequences are likely to enhance motivation when engaging in a protective health behaviour – this is referred to as threat appraisal. • Example: Protection motivation has been significantly correlated with MA to aromatase inhibitors in breast cancer survivors (n=145, r = 0.310; p=0.001).[148]
SCT[144]	• A dynamic and reciprocal model of behaviour change through continuous interaction between individuals and their environment, with a focus on learned behaviour *via* social influences. • SCT explores the capability of an individual to perform a behaviour, which may be influenced through their environment and observational learning e.g., observing the success of someone else adhering to their medicines. • Additionally, outcomes of observational learning may provide positive or negative reinforcement that will influence the likelihood of behaviour change e.g., observation of improved health and wellbeing with MA. • Example: Adherence to anti-retroviral therapy (ART) among individuals living with HIV (n=116) was associated with higher self-efficacy (Adjusted Odds Ratio (AOR) =1.1, p=0.015) and higher perceived normative beliefs about the importance of ART adherence (AOR=1.3, p=0.03).[149]
TPB[145]	• Motivational factors determine the likelihood of performing specific behaviours – referred to as behavioural intentions. • Attitudes shape (favourably or unfavourable) the view of any proposed behaviour change and the associated outcomes e.g., potential risks of starting a new medicine may include side effects, which propagate negative attitudes of MA • Subjective norms (beliefs about peoples' approval/disapproval) and social norms (customary behaviours among groups of people) influence intention related to behaviour change e.g., some cultures may be less accepting of medicines for the treatment and management of chronic conditions that may inadvertently influence an individual's perception of the importance of MA • Example: Attitudes (p=0.02), subjective norms (p<0.01), and perceived behaviour control (p<0.01) significantly predicted MA in a cohort of patients diagnosed with tuberculosis (n=104).[150]

While the TMB help to contextualise drivers of MA, similarly to the framework of unintentional and intentional MA, their application is not without limitation and there remains a lack of useful clinical interventions to address MA based on these and related concepts.[24] Moreover, a SR of TMB and their utility in supporting long-term MA found little empirical evidence of their effectiveness, including the HBM, SCT, PMT and TPB.[151] The authors highlight that while the TMB comprise a wide array of determinants and factors with significant overlap in places, individual components are qualitatively different and to that extent, there is no fully conclusive or holistic model. Therefore, it is a reasonable assumption that if these frameworks struggle with their applicability in an interventional context that this may then also apply to the context of measuring MA and related behaviour, too.

1.5.4 Measures of Medication Adherence

1.5.4.1 Direct Measures

Given the wide array of determinants, factors, and TMB linked to MA, it is somewhat unsurprising that a large variety of methodologies also exist to measure how patients take their medicines. Direct MA methods often rely upon measures of plasma or urine samples to evaluate the concentration of a drug or metabolites associated with a particular pharmacological therapy. Furthermore, drug-adjacent clinical markers can be a useful measure of MA e.g., measurement of serum HbA_{1c} in T2D – MA contributes to a reduction in HbA_{1c} and hence is a useful clinical biomarker for this cohort of patients that can be measured at 3-monthly intervals. Direct measures may have a particular benefit in medicines with a narrow therapeutic index, risk of toxicity, or significant harm caused by non-adherence such as anti-epileptics, theophylline, or Anti-Retroviral Therapy (ART) in HIV, respectively.[152–154] Alternatively, direct observational methods may be employed such as a physical observation of an individual taking their medicines. One common yet perhaps

unrecognised example of this includes the supervision of methadone consumption as part of treatment for heroin dependency in community pharmacies across the UK.[155] While these measures provide a predominantly objective value of MA, serum monitoring/urinalysis are neither systematically cost-effective nor easy to implement. Similarly, direct observation requires a large time cost from both patients and HCPs while providing little to no data around behavioural determinants of non-adherence.[156,157]

1.5.4.2 Indirect Measures

1.5.4.2a Objective Methods

Indirect measures focus predominantly on either objective secondary sources of data from which to derive MA values, or through subjective patient-reported data that provide an insight into an individual's perception of their MA or related behaviours/determinants.[141,157] Electronic Patient Records (EPRs), prescribing data sets, or electronic monitoring systems are some of the most widely used sources for the objective determination of MA (Table 1.11). The electronic record resources provide data including the type of medication dispensed, the quantity, and the date of prescribing/dispensing. From these data, several calculations can be used to assess MA. The Medication Possession Ratio (MPR) and Proportion of Days Covered (PDC) are two of the common methodologies applied to EPRs given their simple design and ease of use. Both calculations determine MA as a proportion of the number of days of medication supplied compared against the interval between medication supplies or a specifically outlined period, as is the case with PDC. Notably, MPR can provide values greater than 1 or 100%, whereas PDC values are capped at either 1 or 100%. While both methods may benefit from ease of use, they are limited by the availability and consistency of the data used to calculate the MA value, which therefore limits their reliability e.g., individuals with multiple prescriptions may have several dispensing dates that can lead to

inconsistent refill interval periods and directly affects the denominator value for an MPR calculation. Furthermore, both methods are prone to overestimation of MA values.[157–159]

Table 1.11 – Objective Methods of MA Measurement

Method	Evaluation/Assessment
Medication Possession Ratio[ab]	$\frac{Number\ of\ days\ supply}{Number\ of\ days\ in\ supply\ period}\ x\ 100\ (\%)$
Proportion of Days Covered[bc]	$\frac{Number\ of\ unique\ days\ supply}{Number\ of\ days\ in\ specified\ period}\ x\ 100\ (\%)$
Medication Events Monitoring Systems	$\frac{Number\ of\ recorded\ electronic\ adherence\ events}{Total\ number\ of\ dosage\ units\ provided}\ x\ 100\ (\%)$
Pill Count	$\frac{Number\ of\ dosage\ units\ dispensed - Number\ of\ dosage\ units\ remaining}{Prescribed\ dosage\ units\ per\ day\ x\ number\ of\ days\ between\ visits}$

Notes: [a]MPR can exceed a value of 1 or 100% as all days are counted e.g., intervals between refills may extend be shorter than the volume of supply;[b]Typical periods or intervals for assessment may include one, six or 12-months;[c]PDC cannot exceed 1 or 100% as the specified period is set as the maximum of unique supply days of medication

Medication Events Monitoring Systems (MEMS) is an example of Electronic Medication Packaging (EMP) and is a reliable and effective method for assessing MA by electronically recording dose events. Dose events recorded electronically through a device, for example when opening the cap of a medicine container, if monitored over a specified interval can provide information on relative MA. Although generally considered as a highly accurate method for determining MA, limitations include over-estimation of MA from accidentally recorded dose events, as well as limited application in real world settings given that the cost of providing MEMS for all patients' medicines would be neither sustainable nor cost effective.[160] Conversely, the Pill Count method has been described as a low-cost and simplified alternative to MEMS by comparing an objective difference in the number of dose

units between dispensing and the following refill or assessment date. While potentially more cost effective, the Pill Count, among other objective MA methods, still provides very little insight into the determinants of MA and related behaviour. Therefore, the application of objective methods in an interventional context may be limited given that they rarely provide an explanation of *why* patients may be non-adherent.[161]Moreover, for count methods, patients are required to bring their pills in for an assessment. These can be easily forgotten creating an additional barrier to measuring MA.

1.5.4.2b Subjective Methods

There are a variety of subjective MA measures including patient diaries, patient interviews (generally clinician-led), and self-reporting methods. They utilise patient recall to provide an estimation of MA – this may be recorded verbally, in a written format or through completion of a questionnaire or survey such as a PROM. Subjective methods are often low cost and require little time to implement within either research or clinical settings to assess MA.[162] While often easy to use, these methods are somewhat unreliable. Limitations include forgetfulness, a bias toward over-estimation of MA when reporting to a clinician or researcher (social desirability, recall, and response bias), and artificial modification of typical medicine-taking behaviour while being observed (known as the Hawthorne effect).[162–164] A review of concordance between self-report (diary, interviews, PROMs) and non-self-report measures (e.g., EPR derived data, MEMS, Pill Count, plasma drug concentrations) of MA was conducted by Garber *et al*.[164] The results demonstrated high concordance (<10% difference) in only 17% (n=15/86) of comparisons between self-report and electronic non-self-report MA measures. However, this increased dramatically to 58% when compared with other objective non-self-report measures. Overall, PROMs demonstrated the most significant and reliable correlations (moderate to high) to non-self-report measures across the comparative studies included in the review, which may again indicate the limitations

associated with less structured recall (diary method) or bias introduced through interviews methods.

Unlike other self-reporting methods, PROMs are usually developed as simple standardised measures that are validated against alternative objective/subjective comparators of MA. Typically, PROMs are validated in a population of patients with a specific diagnosis/condition and consist of a set or sets of questions designed around a designated facet of MA-related behaviour, this is sometimes referred to as a construct, or a domain (group of constructs). PROM responses are often collected as dichotomous data or using a Likert scale methodology to provide a total score. Domains/constructs are often derived from earlier TMB. For example, as the title suggests, the Self-Efficacy for Appropriate Medicine Use Scale (SEAMS)[165] is a 13-item PROM of MA that was developed based on Bandura's[144] conceptualisation of self-efficacy as a determinant of behaviour change within SCT. Similarly, domains associated with perceived threat (HBM), protection motivation (PMT), and control beliefs are reflected in the 18-item Beliefs about Medicines Questionnaire (BeMQ), developed by Horne *et al*,[166] that addresses specific and general statements on medicines e.g., "Medicines do more harm than good" or "Without my medications I would be very ill". While neither the SEAMS nor BeMQ directly evaluate how often or how many medicines a patient has taken, both have demonstrated moderate to strong correlations with objective measures of MA while also providing information on challenges associated with a patient's self-efficacy or certain beliefs about medicines, that can be used to address non-adherence (SEAMS, r=0.573, $p<0.001$; BeMQ, pooled correlation coefficient =0.32).[167,168] Conversely, the Medication Adherence Rating Scale (MARS),[169] Morisky Medication Adherence Scale (MMAS),[170] and Brief Medication Questionnaire (BrMQ)[171] are three example PROMs that elicit responses to medicine-taking behaviour such that their items directly explore whether patients have forgotten to take their medicine(s), miss doses, or if

they have stopped taking their medicine(s) altogether. The latter two PROMs also contain items that explore barriers to adherence, such as side effects and forgetfulness, which may increase the likelihood of discontinuation or a complete failure to initiate treatment. This may be particularly true in individuals with low self-efficacy who feel unable to overcome barriers to MA, as described by the HBM.[147]

It is clear that there are a wide array of PROMs available to assess MA and related behaviour, which are derived from a multitude of TMB and take a variety of approaches. However, despite the significant diversity of PROMs, common themes exist and have been utilised by Nguyen *et al*[172] as a means of classification (Table 1.10). The five categories of PROM comprise three core domains, medication-taking behaviour (e.g., MARS), barriers to adherence (e.g, BrMQ, MMMAS), and beliefs about adherence (e.g., BeMQ) that aggregate as MA. While this approach may be helpful from a taxonomical perspective, it highlights an important limitation – no clear holistic model or gold-standard PROM exists for assessing MA, a sentiment that is echoed across the wider literature.[141,157,173] Given the complex nature of MA, Martin *et al*[174] highlight the necessity of a multi-faceted approach. Previous studies comparing PROMs that measure the same determinant or construct of MA behaviour have demonstrated different results in the same sample population.[175–177] Hence, PROMs that look to address only one or two determinants of MA are unlikely to consider drivers of MA-related behaviour in their totality, which may in part explain the significant lack of successful clinical MA interventions.

1.5.4.3 The SPUR Model

Dolgin[179] emphasises that "existing tools [PROMs] have been criticized as being too restrictive to offer a basis for highly tailored behavioral interventions". The commentary provided by the author also outlines many of the previously cited TMB from this Chapter, as

well as their lack of design to support a multidimensional model, which Dolgin postulates would facilitate a more comprehensive assessment of MA and related behaviours. From this hypothesis, the original SPUR (Social, Psychological, Usage, Rationale) framework was developed with a view to build upon previous TMB, including perhaps most notably the HBM and TPB.[142,145] The original 45-item model was devised following a scoping review of the literature that was conducted to identify PROMs of MA.[180] As part of the review researchers conducted a targeted search of existing tools measuring adherence, related adherence behaviour, and relevant theories on adherence determinants with a predominant focus on chronic conditions. The search was conducted via MEDLINE and included English-language articles published from 2013 to 2018. The search prioritised references that described the development or validation of self-reported measures of adherence behaviour or explicitly referenced at least one TMB relevant to MA. Abstracts and articles were excluded if they fell outside the scope of the research or did not include a self-report measure/TMB.

From the initially identified records (n=311), 128 tools were identified with 27 (21.1%) included the final analysis. The included references were summarised to capture details such as the primary/secondary study objective(s), target audience, number of questions for each model and the constructs measured e.g., self-efficacy. These data were then further interrogated by individually evaluating each item of the selected measures to provide an item-by-item report of the constructs explored within each tool. To help identify which items could be collated within SPUR as a comprehensive model of measuring adherence, items were excluded if they: 1) focused on a specific disease or treatment e.g., insulin 2) duplicates were identified across measures (only one copy was retained if relevant), 3) simply measured missed doses, or 4) were open-ended/qualitative in nature. Following this reduction of items, constructs from the selected items were categorised based on the SPUR framework's four domains (Social, Psychological, Usage, Rational). Similar concepts were then grouped to

ensure a comprehensive framework had been developed across each domain with relevant items sitting within S, P, U and R, respectively for the overall model.

Each domain covers a set of hypothesised factors influencing MA behaviours derived from the models in the scoping review, with 13 constructs extracted in total that were believed to individually and collectively measure MA as an outcome:

- *Social*: subjective norms (1), interpersonal relationships (2).
- *Psychological*: patient–physician relationships (3), health motivation (4).
- *Usage*: intention (5), adherence behaviours/barriers (6), use (7), self-efficacy (8).
- *Rational*: consequence (9), treatment control and necessity (10), prevention/harm (11), knowledge (12), concerns (13).

The number of items for each domain (social (n=6), psychological (n=8), usage (n=13) and rational (n=18)) varied but were collated to develop the initial 45-item questionnaire called SPUR. A set of cognitive interviews were conducted by trained researchers with participants in France (n=15) and the US (n=15) to explore the initial face and content validity of the French and English models of SPUR. More specifically, these interviews explored the clarity and comprehensibility of SPUR in populations of patients diagnosed with chronic conditions, including T2D, breast cancer, and multiple sclerosis. Minor modifications were made to the scoring methodology such that a 5-item Likert scale was implemented *vs* a previous 7-item model. The final model therefore contained 45-items and 5-item Likert scale response for each question. The thesis author was then sponsored to complete a PhD with a view to design and deliver the UK arm of the validation process for SPUR.

1.6 Aim & Objectives

This thesis describes an iterative approach to provide early validation data for SPUR, a holistic and multidimensional PROM of MA in patients diagnosed with chronic conditions. The aim of this thesis is to evaluate the validity of SPUR as a reliable measure of MA that can be applied to real-world health outcomes. The aim can be translated into the following objectives:

1. To explore the scope, validity, and reporting of currently available PROMs of MA (Chapter 2).
2. To examine the validity of the SPUR model in individuals diagnosed with T2D (Chapter 3).
3. To examine the validity of the SPUR model in individuals diagnosed with COPD (Chapter 4).
4. To examine any association between the SPUR model and the risk of hospital readmissions in an acute secondary care setting (Chapter 5).

1.7 Thesis Structure

The thesis consists of the following chapters:

1. This chapter introduced the shift in global population health and the emergence of chronic conditions as a growing public health crisis. Specifically, this chapter discusses some of the most challenging chronic conditions from both a health and economic perspective, namely T2D and COPD. Moreover, Chapter 1 highlights the prevalence and burden of medication non-adherence as a result of rising chronic conditions and current approaches to assess MA and their respective limitations.
2. Chapter 2 describes a SR of currently available PROM of MA for individuals diagnosed with T2D. This chapter looks to address a less-widely discussed topic - the

taxonomical approach to reporting PROMs, their scope and validity with respect to recommended frameworks for the development of PROMs. This Chapter also proposes a novel framework for reporting PROMs within the literature.

3. The third chapter describes the development of the SPUR validation protocol in addition to the iterative approach to provide early evidence of validation for the model in individuals diagnosed with T2D in community pharmacy and secondary care settings.
4. The fourth chapter describes the approach used to provide early evidence of validation for the SPUR model in individuals diagnosed with COPD in secondary care settings.
5. Chapter 5 details the evaluation of the SPUR model as a predictor of readmission and early readmissions of individuals diagnosed with T2D in an acute secondary care setting.
6. This final chapter presents a conclusion to the research with the presentation of summary findings and recommendations for future work.

1.8 Overall Research Methodology

1.8.1 Research Rigour

Two major paradigms, positivism and post-positivism, were adopted by the author to conduct the research described in this thesis. The former paradigm is concerned with realism and objectivism such that social phenomena exist irrespective of the researcher and their position to these phenomena.[182] Positivists seek verifiable evidence through deductive methods where empirical outcomes may be measured using surveys, experimentation, or randomised controlled trials.[183] Similarly, post-positivist approaches seek to identify empirical evidence of causal relationships with the application of methods such as correlational studies.[183] However, post-positivism also recognises the impact of researchers' biases and values,

broader socio-political phenomena, and limitations on methods and processes as a few examples of factors that may influence findings. Hence, the meaning of data is not necessarily inherent, but instead is constructed and interpreted by the researcher.[184] An example of this may be the use of inferential statistics, such as logistic regression, to identify a causal relationship. A positivist approach presents these findings as objective. Conversely, a post-positivist approach presents these findings with consideration for wider socio-cultural influences. Therefore, post-positivists would also support the use of multiple methods to provide a more holistic picture of the phenomena they intend to study – this may also be considered as method triangulation that seeks to reduce bias and improve the reliability and validity of results.

Multiple methods were therefore included in this thesis and are described in Table 1.12. Chapter 2 was conducted as a SR in line with the Preferred Reporting Items for SRs and Meta-analyses (PRISMA) 2020 guidelines.[185] Quantitative methods were conducted throughout the SR to provide evidence of reporting and validity of various PROMs. However, an interpretivist view was taken when examining these data to inform the author's development of a novel research framework. The creation of this framework was guided by their personal interpretation of the most critical issues identified by the SR and their own experience of those issues as a researcher within this field. Throughout Chapters 3-5, a positivist approach was adopted using PROMs in addition to the collection of objective clinical and socio-demographic data for study participants. The PROM and participant data were evaluated as outcomes to determine the relationship between SPUR study factors, as well as the reliability and validity of SPUR and comparative PROMs through psychometric and inferential analyses, such as internal consistency estimates and Chi Square, respectively. A post-positivist approach was taken by recognising the limitations of Chapters 3 and 4. In response, additional inferential methods, such as logistic regression and calibration plots,

were included as part of a real-world outcomes model focused on SPUR and hospital readmission to support the findings of earlier Chapters. Importantly, socio-cultural phenomena were considered as wider influences on the findings of previous work and were therefore collated into the models described in Chapter 5 e.g., the influence of Covid-19.

Pilot studies were conducted to provide evidence of face and content validity for study surveys prior to full-scale data collection. Purposive sampling across community and hospital settings was implemented to ensure that user groups (patients and HCPs) for each intended study setting were included in the review of study materials. Post-pilot a mixture of convenience, snowballing, and purposive sampling methods were used to recruit participants dependent on the study setting, which are described in more detail in Chapters 3 & 4.

Study data were analysed in Statistical Package for the Social Sciences (SPSS). Descriptive statistics were used to report a variety of socio-demographic data collated as a mixture of ordinal and continuous variables. Therefore, a mixture of standard deviation (SD), CI, mode, and mean data were used throughout the thesis to describe socio-clinical factors such as age, gender, BMI and smoking status as a few examples. A large variety of psychometric methods were adopted that included the assessment of validity and reliability criteria for PROMs within the thesis. These methods are described in much greater detail within each respective Chapter. Chi-Square analyses were used to explore the relationship between patient groups as part of known-group validity testing. Data were predominantly non-parametric hence methods such as Spearman's Rho (correlation) and Wilcoxon signed-rank tests (comparing paired samples) were used to describe relationships between relevant study outcomes or groups. Inferential analyses, such as logistic regression, were used to assess the predictive capability of the SPUR model on real-world outcomes, such as hospital readmission.

1.8.2 Credibility

In addition to thoughtful and robust methods, the credibility of research is evaluated through the validity and reliability of the results it produces. These principles are core components of psychometric analyses and hence are reported in detail throughout the thesis. Careful consideration was given to the development of validation methods used when evaluating SPUR and relevant PROMs. Specifically, insight was sought from international guidance including the COSMIN criteria (COnsensus-based Standards for the selection of health status Measurement INstruments)[186] and Food & Drug Administration (FDA) PROM Checklist[187] to capture relevant best practice for the validation of a multidimensional PROM, such as SPUR. From this work, the author decided to include multiple comparative methods such as subjective (PROMs) and objective data (clinical outcomes e.g., HbA_{1c}) to enhance the validity of study findings. Reliability of PROM data was assessed using methods such as Cronbach's α. Furthermore, calibration plots were used to evaluate the reliability of the predictive models developed in Chapter 5.

From a personal practise perspective, the studies conducted in this thesis were subject to NHS ethics review procedures. Hence, the author was required to complete mandatory training on Good Clinical Practice (GCP), General Data Protection Regulations (GDPR), and Health Research Authority (HRA) guidance for research best-practice involving human participants prior to conducting their research. Moreover, research documentation and protocols were scrutinised by external NHS ethics review to determine that the proposed approach for each study was of sufficiently high research quality. This review process was also supplemented by face and content validation of study materials through patient and HCP involvement in pilot studies. The author worked to local Standard Operating Procedures (SOPs) and guidelines produced for NHS research settings, which again provided standardisation of

methods to support the credibility of the research and the findings e.g., patient and study documentation, access to electronic health records (EHRs).

1.8.3 Reflexivity

The author's position and power in conducting their research was considered as part of a reflexive process throughout the PhD. In an attempt to remove bias from the research process, the author attended monthly supervisor meetings to discuss their progress. These meetings were documented, and conversations were steered toward concerns around the author's involvement in the research process itself e.g., influence on findings from external pressures such as attempting to manage deadlines and other professional responsibilities as a pharmacist. Furthermore, once studies were launched, data summaries were shared with a project manager on the research advisory team who could ensure that data collection methods were being conducted in line with the previously submitted protocols. This was also an opportunity for the author to identify new perspectives with a colleague on how best to conduct research considering challenges, such as a slow recruitment period, that may have affected the author's motivation and their approach to the study and participants. The author's power within the patient-clinician dynamic was also considered as a factor throughout the PhD. A particular reflection included whether to introduce themselves as a researcher or pharmacist when speaking to potential participants. Although information about the author's professional background was included on the information sheets used within studies, the former title was chosen during face-to-face introductions given that the author did not want to potentially influence patient's perceptions of a pharmacist being involved in questions around their personal MA.

Table 1.12 –Thesis Structure and Chapter Methodologies

Chapter	**Aims & Objectives**	**Methodologies Used to Collect Data**	**Methodologies Used to Analyse Data**	**Rationale for Methodologies Used**
Chapter 2: A Systematic Analysis of Reviews Exploring the Scope, Validity, and Reporting of Patient-Reported Outcomes Measures (PROMs) of Medication Adherence in Type 2 Diabetes (T2D)	This chapter aimed to explore the scope, validity, and reporting of currently available PROMs of MA in T2D. Objectives: - To evaluate the validity of PROMs reported in systematic reviews (SRs) - To examine the different types of PROMs reported e.g., adaptations, and the way they are reported - To explore the association between bibliometrics data and validity/reporting outcomes - To evaluate the uptake of the COSMIN framework	Preferred Reporting Items of Systematic Reviews and Meta Analyses (PRISMA).[185]	The uptake of the COnsensus-based Standards for the selection of health status Measurement Instruments (COSMIN)[186] criteria was assessed for each included SR. Data were collected in Microsoft Excel prior to an export to the Statistical Package for Social Sciences (SPSS) for further analysis. Non-parametric correlation analyses (Spearman's Rho) were conducted to explore the association between journal quartile ranking and the number of errors relating validity/reporting of PROMs.	PRISMA contains a set of guidelines for reporting the results of both SRs and meta-analyses. This methodology is recognised as a stepwise framework that researchers can employ to improve the transparency and reproducibility of their SRs. The COSMIN criteria are a set of standards for evaluating the methodological quality of studies on measurement properties of patient-reported outcome measures (PROMs). Spearman's Rho was selected due to the non-normal distribution of the quantitative data collected for each SR included in the analyses.
Chapter 3: SPUR: Psychometric properties of a patient-reported outcome measure of medication adherence in Type 2 Diabetes (T2D)	This chapter aimed to provide evidence of the validity of the SPUR model in individuals diagnosed with T2D. Objectives: - To evaluate the psychometric properties of SPUR in patients diagnosed with T2D from community and hospital settings - To explore the associations between SPUR (adherence) and other socio-demographic/socio-clinical factors - To compare SPUR as a multidimensional model to other PROMs validated in T2D	Patient Pilot Study (n=15) – 45-item original SPUR model (1-5 Likert-scale items across the four major SPUR domains) in addition to socio-demographic questions (n=4), Likert-scale items to assess acceptability/face and content validity (n=5) and items relating to general feedback and HbA_{1c} testing (n=3). HCP Pilot Study (n=6) – 45-item original SPUR model in addition to socio-demographic questions (n=4), Likert-scale items to assess acceptability/usefulness (n=5) and a single item relating to general feedback. Validation a Medication Adherence Tool in Type 2 Diabetes (VMATT2)	Data were collected in Microsoft Excel prior to an export to SPSS for further analysis. For psychometric analysis, an exploratory factor analysis approach was undertaken including principal axis factoring with a direct oblimin rotation. Cronbach's alpha was calculated to determine internal consistency estimates for the SPUR model. Scoring methodologies for each specific comparator PROM and SPUR were followed, prior to conversion to percentage values (n=x/100%) that could then be correlated using a non-parametric analysis (Spearman's Rho).	PROMs provide a standardised approach to data collection that can be replicated across different populations/settings for comparison and inter-group analysis. The psychometric methods and correlation analysis to determine for example construct/known group validity used in this study were derived as part of a bespoke methodology formed around international guidelines such as COSMIN/Food and Drug Administration (FDA) PRO validation criteria. A Shapiro-Wilk test for normality indicated that the data for all relevant analyses were non-normally distributed, hence non-parametric methods were applied throughout.

		Study (n=378) - 45-item original SPUR model in addition to socio-demographic questions (n=4) and items relating to clinical characteristics that were either self-reported or derived from the patient's medical record/summary care record where applicable e.g., HbA_{1c}, Body Mass Index, the number of prescribed medicines, Medication Possession Ratio. Three comparator PROMs were included: - Beliefs about Medicines Questionnaire (BeMQ).[188] - Medication Adherence Rating Scale (MARS). [189] - Diabetes Treatment Satisfaction. Questionnaire (DTSQ).[190] Sample population (Patient Pilot & VMATT2) – Adult patients diagnosed with T2D recruited from community pharmacies and Kingston Hospital. Sample population (HCP Pilot) – Community pharmacists and pharmacists with medicines optimisation experience. Recruitment and data collection were conducted between August 2019 and May 2021 using a convenience and snowball sampling approach (community arm and Patient/HCP Pilot) in addition to purposive sampling for the hospital arm. Local and national NHS Ethics were sought as appropriate for the studies.	Other non-parametric methods were applied to explore between group differences (e.g., differences in SPUR score between community and hospital patients, differences based on socio-demographic data such as gender) with Wilcoxon signed-rank tests and Kruskal Wallis H tests used for variables with two groups, or more than two groups, respectively. Effect sizes were determined using Cohen's d or Glass's Δ. For all relevant analyses, $p<0.05$ was considered significant.	Two different recruitment strategies were selected included snowball/convenience and purposive strategies for community and hospital settings, respectively. Specifically, purposive sampling was selected for hospital patients in line with PRO validation guidance whereby the target patient group can be recruited in a timely manner, unlike in community pharmacy settings where patient engagement is randomised and patient-led based on those that attend the setting. The BeMQ, MARS and DTSQ have been validated in populations living with T2D. Specifically, the BeMQ provides comparative insights on Rational and Psychological domains for SPUR, MARS for Usage, and finally DTSQ as a pseudo-comparator for Social while providing contextual information about overall treatment satisfaction.
Chapter 4: SPUR: Psychometric properties of a patient-reported	This Chapter aimed to provide evidence of the validity of the SPUR model in individuals diagnosed with COPD.	Patient Pilot Study (n=8) – 45-item original SPUR model in addition to socio-demographic questions (n=4), Likert-scale items to assess	Data were collected in Microsoft Excel prior to an export to SPSS for further analysis.	As indicated under Chapter 3, PROMs provide a standardised approach to data collection that can be replicated across different populations/settings for

outcome measure of medication adherence in Chronic Obstructive Pulmonary Disease (COPD)	Objectives: - To evaluate the psychometric properties of SPUR in patients diagnosed with COPD from a hospital setting - To explore the associations between SPUR (adherence) and other socio-demographic/socio-clinical factors - To examine the cross-cultural validity of the SPUR model in a new patient population - To explore the sensitivity, specificity, and adequacy of the SPUR model	acceptability/face and content validity (n=5) and an item relating to general feedback. Validating a Medication Adherence Tool in COPD (VMATC) Study (n=100) - 45-item original SPUR model in addition to socio-demographic questions (n=7) and items relating to clinical characteristics that were either self-reported or derived from the patient's medical record/summary care record where applicable e.g., smoking status, Body Mass Index, the number of prescribed medicines, Medication Possession Ratio. One comparator PROM to assess adherence was included, with the addition of the COPD Assessment Test (CAT) to explore known group validity: - Inhaler Adherence Scale (IAS).[191] - COPD Assessment Test.[127] Sample population (Patient Pilot & VMATC) – Adult patients diagnosed with COPD. Recruitment and data collection were conducted between Feb 2020 and December 2021 using a convenience and snowball sampling approach for the community arm Patient Pilot, while a purposive sampling approach was implemented for the main hospital study (VMATC) Local and national NHS Ethics were sought as appropriate for the studies.	For psychometric analysis, both an exploratory factor analysis and partial confirmatory factor analysis approach were undertaken. Cronbach's alpha was calculated to determine internal consistency estimates for the SPUR model. Scoring methodologies for the IAS and SPUR were followed, prior to conversion to percentage values (n=x/100%) that could then be correlated using a non-parametric analysis (Spearman's Rho). Other non-parametric methods were applied to explore between group differences (e.g., differences based on socio-demographic data such as gender) with Wilcoxon signed-rank tests and Kruskal Wallis H tests used for variables with two groups, or more than two groups, respectively. A Chi-square analysis was used to explore the differences in groups of patients divided by their COPD symptoms severity (assessed using the COPD Assessment Test) *vs* adherence as defined by the SPUR model. For adequacy testing, sensitivity and specificity analyses were conducted with a combination of Receiver Operator Characteristic (ROC) curve and Area Under the Curve (AUC) calculations. For all relevant analyses, $p<0.05$ was considered significant.	comparison and inter-group analysis. The psychometric methods and correlation analysis to determine construct/known group validity used in this study were derived as part of a bespoke methodology formed around international guidelines such as COSMIN/FDA PRO validation criteria. Specifically, additional hypothesis testing was conducted to explore the cross-cultural validity of the SPUR model in the absence of strong a-posteriori evidence. To this extent, partial confirmatory factor analysis was conducted in addition to exploratory factor analysis to provide a more robust assessment of SPUR in the new patient population. Again, purposive sampling was selected for hospital patients in line with PRO validation guidance whereby the target patient group can be recruited in a timely manner. This was particularly poignant given the impact of the Covid-19 pandemic on the recruitment of this study. The IAS and CAT were selected due to their validity in patients living with COPD to provide evidence of construct and concurrent validity.
Chapter 5: The Real-World Application of SPUR-27 as a Predictor of Admission & Early	This Chapter aimed to determine the association between the SPUR model and the risk of hospital readmissions in an acute secondary care setting.	VMATT2 Readmission (n=200) – Revised SPUR-27 model data were derived from the previous VMATT2 study following iterative scale development methods in Chapters 3/4.	Data were collected in Microsoft Excel prior to an export to SPSS for further analysis.	An observational study design was selected to build upon the cross-sectional evidence base provided in Chapters 3 and 4. While correlation analyses are useful, they provide little support to determine

Readmission in Type 2 Diabetes	Objectives: - To examine real-world evidence for SPUR and the association to clinical outcomes such as general admission and early readmission risk in patients living with T2D - To evaluate other socio-demographic/clinical determinants of admission/readmission risk among hospital patients diagnosed with T2D - To compare the predictive capability of admission/early readmission of SPUR to other PROMs of adherence and related behaviours in patients living with T2D	An observational methodology to data collection was implemented to capture admission data across a 12-month duration, which included a 6-month admission history prior to participation in the original VMATT2 study, as well as 6-month follow-up period. Additional PROM data were derived from the previous VMATT2 cohort, which included BeMQ, MARS, DTSQ scores as well as objective measures HbA_{1c}. Other covariates e.g., the Index of Multiple Deprivation (IMD) were derived by calculating the value from the patient's postcode to provide a measure of deprivation across the cohort. Admission data were derived from the Trust's Electronic Health Record (EHR) system. The sample population included the patients (n=200) previously recruited for the hospital arm of the VMATT2 study. Recruitment procedures were previously conducted during VMATT2, whereby participants provided consent to also participate in the observational arm of the study (VMATT2 Readmission). Recruitment for the original VMATT2 study (hospital arm) cross-sectional phase began in January 2020, with the final participants being recruited in October 2021. As a result, the total observational period for data collection spanned from July 2019 to March 2022 National NHS Ethics were sought as appropriate for the study.	Variables were collected and grouped as either count (the number of instances e.g., admissions) or binary (e.g., did the patients have an admission?) outcomes. Poisson or negative binomial modelling was employed for count variables. For binary outcomes, logistic regression models were used, incorporating the same set of covariates. To reduce model bias, Firth's penalized maximum likelihood estimator was employed. Goodness-of-fit and calibration modelling were undertaken, with the latter using ROC-AUC measures to explore the model's discriminant ability.	causation, which may be more useful when constructing clinical interventions. Firth's penalized maximum likelihood estimator has a particularly stable performance, even at low sample sizes, hence was selected for this study. Clinical outcomes such as general admission risk and early readmission were chosen as model to demonstrate real-world evidence given their strong link to health-economic impact. Moreover, these outcomes have previously been linked to medication adherence. Therefore, these outcomes provided a suitable evidence base to compare a multidimensional model such as SPUR to other PROMs that measure adherence related behaviour. Similarly to adherence, other socio-demographic/clinical determinants of admission risk such as deprivation (IMD) were included to build a more holistic predictive model. Calibration is an often-overlooked aspect of predictive modelling. In fact, models that possess good discriminant validity may also provide poorly accurate risk-estimates making them less suitable for clinical decision making. Therefore, ROC-AUC modelling for binary outcomes were included in the study.

Chapter 2: A Systematic Analysis of Reviews Exploring the Scope, Validity, and Reporting of Patient-Reported Outcomes Measures of Medication Adherence in Type 2 Diabetes

2.1 Introduction

2.1.1 A Brief History of Patient-Reported Outcome Measures

In their review, Churruca *et al*[192] noted that the term "patient-reported outcome" (PRO) is a relatively new term used to describe PROMs and related measures. PROMs are self-reported assessments that ask patients about their health, symptoms, and quality of life, with the aim of capturing the patient's perspective on their own health status. The use of PROMs has become increasingly popular in recent years, with some linking their adoption to the greater importance being placed on patient and public involvement in research.[193] One of the earliest examples of a PROM was the Sickness Impact Profile (SIP), developed in 1976 by Bergner *et al*.[194] The SIP was a self-administered questionnaire designed to assess the impact of illness on a person's daily life with a view to support the evaluation of health care service outcomes. Notably, these more nascent iterations of what we today refer to as PROMs were often described as 'health status measures'.

Over the next 10-15 years, researchers began to develop disease-specific PROMs, such as the Arthritis Impact Measurement Scales (AIMS)[195] and the Functional Assessment of Cancer Therapy (FACT).[196] These instruments were designed to measure the impact of specific disease-related outcomes, which popularised their use in settings such as clinical trials and outcomes research and helped to define the two major categories of PROM used in modern practice – generic and condition-specific.[192] With more widespread adoption across the 1990s and early 2000s, the scope of PROMs and their relation to a broader set of health related outcomes was expanded. For example, the development of the Short Form-36 (SF-36) Health Survey Questionnaire demonstrated significant (p<0.05) correlations between the

PROM and other measures of physical activity (r=0.63) and general health (r=0.47) in a cohort (n=90) of patients surviving 1-year post-stroke.[197] However, this PROM also identified correlations in social function (r=0.33) and mental health (r=0.29), thus providing a contextual profile of individuals who completed the SF-36 as part of the study. The evolution of PROMs extends into their applications beyond measuring patient health status alone. The EuroQol-5D, otherwise known as the EQ-5D, is a preference-based measure that assesses HRQoL. Solberg *et al*[198] provided a validation model for the EQ-5D with the potential to explore cost-utility analyses through reporting of health state values and outcomes of patients undergoing lower-back surgery. These data have informed decision making among NHS stakeholders responsible for care budgets over the last two decades.[199] Hence, PROMs have grown to play an important role in identifying not only patient-related outcomes, which improves patient-physician communication and quality of care, but also providing specific value to systems that care for these patients through health economic modelling, as just one example.[200,201]

2.1.1.1 Psychometric Properties of PROMs

Psychometric properties can be understood as evidence of the usefulness and efficacy of PROMs to determine patient-reported outcomes. These properties may include measures such as reliability, validity, responsiveness, and interpretability that comprise several components as part of a holistic PROM assessment. The COSMIN (COnsensus-based Standards for the selection of health status Measurement Instruments) criteria[186] are a set of internationally recognised standards for the evaluation of PROMs that provide useful definitions for each property. The most recent update to the checklist, titled 'COSMIN Study Design checklist for Patient-reported outcome measurement instruments' was developed by Mokkink *et al*[186] in 2019 and is derived from both the original COSMIN checklist[202] and COSMIN Risk of Bias checklist.[203] An abbreviated summary of measurement properties and

recommendations/assessment approaches for study design derived from the COSMIN criteria are described in Table 2.1. For each section of the criteria, implementation or reporting of particular analyses or data are rated as ‘very good’, ‘adequate’, ‘doubtful’, ‘inadequate’, or ‘not applicable’. For the purposes of this introduction, only ‘very good’ or ‘adequate’ core criteria are described in Table 2.1. While not necessarily considered within the core criteria, the concept of interpretability is also an important factor when assessing PROMs. Interpretability can be defined as the degree to which one can assign qualitative meaning - that is, clinical or commonly understood connotations – to a PROM’s quantitative scores, change in scores, or content.[204] Put simply, interpretability considers the perceived relevance or relatability of those using the PROMs such as patients, clinicians, and/or researchers.

These properties help to ensure that the PROMs are effective in assessing patient outcomes, supporting clinical decision-making, and improving patient care. While standards such as the COSMIN criteria exist, neither their implementation nor the reporting of psychometric properties are universal. Furthermore, aside from issues relating to the standardisation of the reporting of psychometric properties of PROMs, even the reporting of the actual PROMs from a taxonomical perspective presents challenges due to the use of different terminology that make it difficult to find the relevant models. A recent 2022 SR of PROMs of HRQoL for individuals living with T2D identified that <30% (n=41/150) of subscales from a pool of 54 unique PROMs had adequate evidence of content validity.[205] In fact, a significant number of PROMs across a wide range of chronic conditions lack evidence of reliability and validity, reducing their usefulness and efficacy in determining patient-reported outcomes; this may specifically limit their application within clinical and other related health settings.[204,206–208]

Table 2.1 – A Summary of Measurement Properties & Study Design Recommendations Using the COSMIN Checklist[186]

Core Criteria	Recommendations/Assessment Approach
General Study Design	• A research aim should be clearly described including the name/version of the PROM, the population and measurement property of interest. • The measured construct is clearly described. • The development process (e.g., PROM development, target groups) are clearly described. • The origin of the construct (e.g., theoretical framework) should be clearly described. • The structure and scoring are clearly reported. • Existing evidence of PROM quality is reported. • The description/context of use for the PROM is clearly described. • Inclusion/Exclusion criteria for the target population are defined. • The sample selection method is reported. • Evidence that the sample population is reflective of the target population
Content Validity	• Definition - the degree to which the content of the PROM reflects the construct it intends to measure. • Appropriate qualitative/quantitative evaluation of patient/HCP perceived relevance and interpretability of the PROM. • Healthcare professionals should come from relevant backgrounds, with mixed expertise if appropriate. • Appropriate skilled interviewers/researchers should be involved, with at least two contributing to the analysis.
Structural Validity	• Definition - the degree to which the scores of an instrument are an adequate reflection of the dimensionality of the construct to be measured. • Factor analysis should be conducted on the entire instrument when it is considered to be multidimensional. • Classical Test Theory (CTT) recommendations include the use of Confirmatory or Exploratory Factor Analysis (CFA or EFA) • The sample size for Factor Analysis (FA) should be ≥7 times the number of items or >100. • The management of missing items are clearly described. • Models may be described as reflective or formative, with the former being indicative of a PROM where all items are a manifestation of the same underlying construct. Structural validity applies to reflective models.
Internal Consistency	• Definition - the degree to which items within a scale are related to each other. • Appropriate for reflective models where internal consistency should be assessed for each scale – this may apply to each subscale within a multidimensional model. • A very good sample is that with ≥100 participants. • Cronbach's α or ω are reported for scores using continuous data.
Cross-cultural Validity	• Definition – the degree to which items of a PROM behaves similarly in different populations, such as differences in socio-demographic characteristics (ethnicity) or language. • Group variables are clearly described. • Perform Multi-Group CFA (MGCFA) where appropriate with the sample exceeding 7 times number of items and ≥100 patients.
Reliability & Measurement Error	• Definition – the degree of score consistency over time. • Use of independent administrators with stable participants at different time intervals to repeat the measurement. • At least two measurements should be used. • For continuous scores, Standard Error of Measurement (SEM) will be calculated (measurement error). • For continuous scores, Intraclass Correlation Coefficients (ICCs) will be calculated (reliability).
Criterion Validity	• Definition – the degree to which the PROM is predictive of the measurement construct. • Typically, criterion validity is explored when a gold standard comparator is available – in this instance, the gold standard comparison would be a long *vs* short form of the PROM. • At least 50 patients in the smallest group for analyses.

	• For continuous scores, correlations or Area Under the Curve (AUC) will be calculated (more specifically AUC will be demonstrated for a Receiver Operator Characteristic (ROC) curve).
Hypothesis Testing (Construct Validity)	• Definition – the degree to which the PROM measures the construct it is intended to measure. • Construct validity contains further sub-analyses and definitions including: o Convergent Validity – comparison with other outcome measurements. o Discriminant or Known-group Validity – comparison between subgroups. o Other outcome measurements are assumed to be of good quality. • For convergent validity, the below should be considered: o Hypotheses should be formulated prior to testing, with expected directions and strengths of correlations declared prior to analysis. o Comparator instruments should be clearly described in terms of the constructs they intend to measure. o Comparator instruments should demonstrate sufficient measurement properties. o A sample of ≥100 should be implemented. o The PROM and comparators will be co-administered. • For discriminant or known-group validity, the below should be considered: o Hypotheses should be formulated prior to testing, with expected directions and strengths of correlations declared prior to analysis. o Subgroup characteristics (e.g., disease state, sociodemographic characteristics) should be defined. o A sample of ≥100 should be implemented per subgroup.
Responsiveness	• Definition – the degree to which the PROM can detect changes in health status among the sample. • Depending on the availability of a gold standard or other comparative measures, a criterion or construct validity approach can be taken. • Implement an appropriate time interval for repeating measurements prior to comparison of changes among subgroups. • Depending on the approach (criterion *vs* construct), either ≥50 or ≥100 individuals should be within the subgroups, respectively. • Sample interactions between testing intervals should be declared e.g., an intervention took place.

Abbreviations: PROM, patient-reported outcome measure; HCP, healthcare professional; CTT, classical test theory; CFA, confirmatory factor analysis; EFA, exploratory factor analysis; FA, factor analysis; MGCFA, multi-group confirmatory factor analysis; SEM, standard error of measurement; ICC, intraclass correlation coefficients; AUC, area under the curve; ROC, receiver-operator characteristic/curve

2.1.1.2 The Application, Adaptation and Psychometric Properties of PROMs in T2D

Though initially validated in English with a cohort of patients diagnosed with hypertension, the MMAS has become one of the most widely adopted PROMs for measuring MA in T2D as a pseudo 'gold-standard' model, as well as a range of other chronic conditions owing to its short and simple design.[209] The original tool contained 4-items (MMAS-4), which was later developed into MMAS-8, which consists of eight questions that directly assess medication-taking behaviour through an evaluation of a patient's forgetfulness, carelessness, and intentional non-adherence.[170] Higher MMAS-8 scores, typically defined using a ≥6 cut-off, have been associated with improvement in glycaemic control. One example is provided by Wong *et al*[210] in their evaluation of MA using MMAS-8 in a cohort of 585 Chinese

participants with T2D recruited from outpatient settings in Hong Kong. The study demonstrated that higher MMAS-8 scores had a significant negative correlation with HbA_{1c} (−0.095; 95% CI −0.164, −0.026; p=0.007). In contrast, poor MA, defined as a score <6, has been associated with complications related to poor glycaemic control including nephropathy and retinopathy.[211,212] Notably, Wong *et al*[210] implemented the Chinese adaptation of the original English MMAS-8 questionnaire, which has demonstrated reasonable psychometric properties such as moderate internal consistency (α=0.65), strong concurrent validity (r=0. 75, p<0.01) with the Visual Analogue Scale (VAS), as well as group validity with significant associations between MMAS-8 categories and HbA_{1c} categories using Chi-Square analysis ($\chi 2$ = 21.63; p<0.001) to provide further evidence that higher adherence was linked to improved glycaemic control.[213]

MMAS-8 is a brief tool that has widespread application across a range of chronic conditions such as hypertension, T2D, and oncology. [212,214,215] While no comprehensive list of adaptations has been reported in the literature, it is unsurprising that many translations have been documented for the model.[212,214,215] Though, despite its translation into languages such as Spanish, Korean, and Portuguese, the PROM has not always demonstrated suitable cross-cultural validity.[214,216,217] For example, in a report on the validation of the Korean MMAS-8, Weon-Young *et al*[216] identified a somewhat inadequate (α<0.7)[218] estimate of internal consistency (α=0.66) as well as a significant ceiling effect, with almost one third (30.5%, n=98/321) of participants recording a maximum score of eight with the tool. Confirmatory Factor Analysis (CFA) was conducted to evaluate the goodness-of-fit indices including: goodness-of-fit index (GFI); the root mean square error of approximation (RMSEA); the normed fit index (NFI); the non-normed fit index (NNFI); the relative fit index (RFI) and the comparative fit index (CFI). The indices assess the degree of similarity between the model's predictions and the actual data. Acceptable cut offs are as follows: GFI, NFI, NNFI, RFI and

CFI >0.95, and RMSEA<0.06.[186] Overall, the Korean version of MMAS-8 demonstrated a poor fit (GFI 0.82; RMSEA, 0.17; NFI, 0.47; TLI, 0.44; RFI, 0.47; CFI, 0.49). Similarly, the Spanish MMAS-8 was subject to concerns regarding the validity of its model that demonstrated poor internal consistency (α=0.40; 95% CI, 0.28, 0.52). However, both the Korean and Spanish adaptations reported Internal Consistency Correlations (ICCs) >0.7, which is deemed as an acceptable indicator of reliability,[186] yet only the former model was considered as a suitable measure of MA. Notably, neither CFA nor ceiling effects were reported for the Spanish version of MMAS-8. This incongruence in both the reporting and Interpretation of psychometric properties of MMAS-8, particularly with attempts at Cross-Cultural Adaptation (CCA), demonstrates a lack of standardisation. As previously highlighted, this may limit application of such models within clinical settings, but also creates difficulty for researchers looking to systematically assess the evidence of psychometric properties of PROMs within the literature.

Several other validated PROMs have been designed to assess MA in patients living with T2D and have shown a range of psychometric properties, including the Summary of Diabetes Self-Care Activities (SDSCA),[219] the MARS-5/10[220] (including the shorter 5-item and longer 10-item adaptations), and the Adherence to Refills and Medication Scale (ARMS).[221] Furthermore, though disease specific models, such as the Diabetes Treatment Satisfaction Questionnaire (DTSQ),[190] may not directly explore MA behaviour, they have been correlated to other MA measures. For example, higher DTSQ scores correlated significantly and positively with MMAS-8 (r=0.299, p<0.001) in a cross-sectional study of primary care patients (n=319) living with T2D in Egypt.

While not directly examining MA, MA-adjacent PROMs e.g., DTSQ, can help to identify a broader set of determinants of MA-related behaviour. However, it is worth noting that for these PROMs and those that specifically address MA, even within the same population there

can be moderate to high variability when comparing results, limiting their reliability and validity.[175,176] Moreover, even instances where evidence is provided for the psychometric properties of PROMs, few conditions have established a clear link between specific levels of MA and clinical outcomes.[172] Conversely, some widely implemented PROMs of MA have not been validated against clinical outcomes or other direct methods of measuring MA, perhaps emphasising poor uptake of frameworks such as the COSMIN criteria.[172,186,192]

2.1.2 Rationale

Previous SRs have attempted to assess the range of PROMs or specific PROMs used in T2D; however, there is a lack of commentary on the standardisation of how these PROMs are reported or evaluated for validity. Furthermore, to my knowledge there is no published SR that explores to uptake of a framework such as the COSMIN criteria in T2D.

2.1.3 Aims & Objectives

This study aimed to conduct a systematic analysis in the form of a SR of other published SRs of PROMs of MA in T2D with the goal of capturing the widest range of tools and addressing previous concerns regarding the impact of taxonomy on reporting. The review also aimed to examine the use of validity and reliability criteria in PROM reporting, including an investigation of COSMIN implementation across the literature. Therefore, the objectives of this chapter were as follows:

- To evaluate the validity of PROMs reported in SRs
- To examine the different types of PROMs reported e.g., adaptations, and the way they are reported
- To explore the association between bibliometric data and validity/reporting outcomes
- To evaluate the uptake of the COSMIN framework

2.2 Methods

2.2.1 Literature Review

This SR was conducted in January 2022 in accordance with the PRISMA 2020 guidelines.[185] The following databases were included in the search to ensure all relevant SRs were identified prior to analysis: PubMed, EMBASE, CINAHL, Cochrane Database of SRs and Web of Science (WOS). A database search strategy was developed (Table 2.2), which included the use of Medical Subject Headings (MeSH) terms that are used to catalogue and index specific vocabulary or terminology. The search strategy aimed to identify SRs reporting on PROMs of MA in people living with T2D. Key terminology and associated synonyms or related terms that were relevant to the condition of interest (T2D), outcomes (MA), and methods (PROMs) were extracted from either the title or abstract (referred to as [Title/Abstract]) where applicable to the search engine. Furthermore, depending on the database search engine, filters such as "SR", "Literature Review", or "Review" were applied to improve the specificity of search engine results prior to the screening process. SRs were considered eligible for screening if they were peer reviewed, published in English, and reported between database inception and December 2021. Individual references within the included SRs at the screening stage were reviewed for incidental inclusion of other eligible SRs prior to further analysis.

Table 2.2 – Database Search Strategy

Disease/Condition Terminology	Diabetes Mellitus"[Mesh] OR "diabetes mellitus"[Title/Abstract] OR "t2dm"[Title/Abstract] OR "NIDDM"[Title/Abstract] OR "type 2 diabetes" [Title/Abstract]
Included Search Terminology	persisten* OR ("Patient Compliance") Or ("Patient compliance" OR "User compliance" OR "patient adherence" OR "treatment adherence" OR "Patient adherence" OR "Patient cooperation" OR "Patient non adherence" OR "Patient non compliance" OR "Patient nonadherence" OR "Patient non-adherence" OR "Patient noncompliance" OR "Patient non-compliance" OR "adherence to therapy" OR "adherence to treatment" OR "compliance to therapy" OR "compliance to treatment" OR "therapy adherence" OR "therapy compliance" OR "treatment adherence" OR "treatment compliance" OR "dosage adherence" OR "dosage compliance" OR "dose adherence" OR "dose compliance" OR "dosing adherence" OR "dosing compliance" OR "drug adherence" OR "drug compliance" OR "drug intake compliance" OR "drug regimen adherence" OR "drug regimen compliance" OR "medication adherence" OR "medication intake adherence" OR "adherence to pharmacotherap*" OR "compliance with pharmacotherap*") (patient reported*) or patient-report* or self-report* (Questionnaires OR interview) or (instrument* OR scale* OR Questionnaire* OR measure* OR methods OR outcome measurement* OR (test OR tests)) or tool* or survey* or PROM*
Publication Type	Review/SR/Literature Review
Publication Date	No origin date set (Database Inception) – December 2021
Population	Human - Adult

Abbreviations: NIDDM, Non-insulin Dependent Diabetes Mellitus

2.2.2 Selection of SRs

A specific set of additional inclusion and exclusion criteria were applied to the SR selection process. Studies including ≥1 chronic condition were included if the cohort of patients diagnosed with T2D could be distinguished to distinctly reflect the use of a specific PROM among that patient population e.g., SRs may have reported on a cohort of individuals either with T1 or T2D, however if a clear sample size for the T2D population and PROM associated with that subsample were reported, then the SR was considered eligible for inclusion. As outlined in Table 2.2, the search strategy aimed to specifically highlight SRs containing adult populations only, hence any SR pertaining solely to paediatric populations were excluded. However, similarly to the principle applied to SRs that comprised populations of patients with several different conditions, if a paediatric population was reported but a sample size and distinct PROM could be distinguished for the adult population(s) with T2D, then the SR was considered eligible for inclusion. SRs that examined MA to oral antiglycaemics (OAs)

and/or insulin or related pharmacological agents with a different method of administration were included in the analysis. SRs that included studies not published in English that met the above inclusion criteria were considered eligible. Moreover, only SRs that clearly attributed an eligible PROM to a specific included study were considered relevant for systematic analysis. Protocols and studies that included a T2D PROM, but not specifically for MA e.g., knowledge, were excluded from further analysis.

2.2.2.1 Initial Screening Protocol

Independent screening of abstracts and titles was initially conducted by the author and the second supervisor to identify appropriate SRs based on the outlined inclusion and exclusion criteria. The same approach was applied to full-text publications. Discrepancies between either researcher during the screening process were presented to the first supervisor for review and a final decision on inclusion/exclusion of the SR.

2.2.3 Systematic Analysis

As part of the systematic analysis, a novel assessment framework (Figure 2.1) was devised to classify data derived from the SRs into three major domains including: the types of PROMs reported in studies across all the included SRs, a two-tier assessment of PROM validity for individual studies and SRs (validity assessment), and finally a reflection of eligible PROM reporting for individual studies and within each SR (reporting assessment). A bibliometric assessment was conducted at SR level only. Several other metrics such as SR descriptions and their objectives, often defined as primary and secondary outcomes, were also assessed and reported.

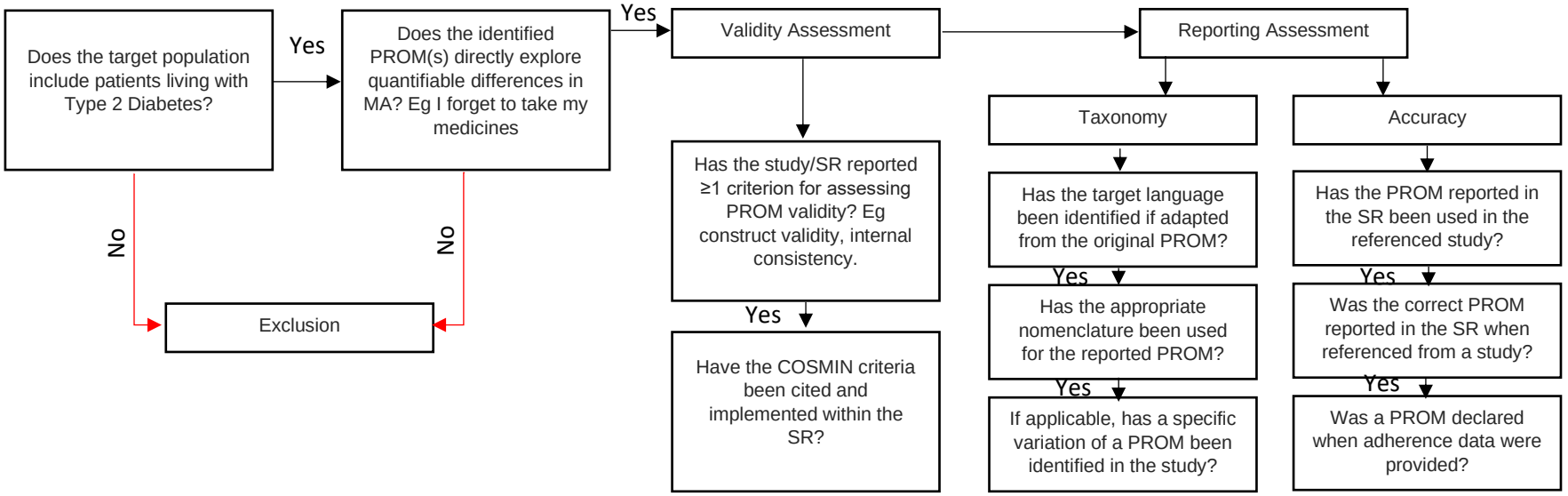


Figure 2.1 - Flow chart of the review assessment framework.

2.2.3.1 Individual Study PROM Assessment Criteria

Within each SR, the individually reported studies were assessed to determine their suitability for inclusion in the broader analysis. Only studies that reported PROMs of MA in patients living with T2D were considered eligible. More specifically, studies were only considered for inclusion if the PROM directly assessed medication-taking behaviour, for example, valid PROM items may include "I forget to take my medication" or "rate how many days in a week you take your medicine". Studies that reported PROMs that solely explored correlated constructs, factors, or determinants of medication-taking behaviour such as beliefs about medicines, treatment satisfaction, and disease knowledge were excluded from further analysis. These data were then synthesised to reflect the range of tools included across all SRs.

2.2.3.2 Validity Assessment Criteria

A two-tier approach was applied to examine both SRs and individual studies as part of the assessment for PROM validity. The tier one assessment was conducted at the SR level. Validity reporting was considered appropriate if ≥1 of the following criteria had been explored as part of the SR: internal consistency, reliability, measurement error, content validity (including face validity), construct validity (including structural validity, hypotheses testing and cross-cultural validity), criterion validity, responsiveness, and interpretability. With the exception of one case, all SRs were published after 2010, which was the year that the COSMIN criteria were first reported. The validity assessment therefore included an evaluation of both the uptake and implementation of the COSMIN criteria across all included SRs published after 2010. The second tier of the validity analysis applied to individual studies reported within each SR. Specifically, studies were examined to determine both the

implementation and validity of the reported PROM(s). PROMs were classified as lacking validity if any of the following were identified:

- Inappropriate translation of a PROM into a new target language(s) – this may include the lack of appropriate translation methods being used or described e.g., valid methods include forward and backward translation of a PROM using a native speaker in addition to reporting ≥1 validation criterion.
- Inappropriate application of a PROM in a new target condition(s) without reporting ≥1 validation criterion as evidence of cross-cultural validity.
- Application of a PROM (provided with no reporting of the target language for the study population) whilst using a PROM that did not have a translated adaptation relevant to that population.

These data were synthesised as part of a quantitative assessment to produce a percentage value that reflected the proportion of PROMs without adequate validity over the total number of eligible PROMs reported within each SR.

2.2.3.3 Reporting Assessment Criteria

The final major domain assessed as part of the systematic analysis was the reporting of PROMs. Despite the availability of the COSMIN criteria as an example of a framework that supports the evaluation, selection, and some specific reporting components of PROMs, evidence of general reporting standardisation for PROMs across the literature is lacking. Before conducting the analysis, a rudimentary framework to assess PROM reporting was developed as a method to standardise evaluation of SRs and studies included as part of this review. The framework covered several criteria:

1. Taxonomy

a. Has the language of the PROM been defined if translated or used in a target language different from the original PROM?
b. Has the correct nomenclature of the PROM been reported in the SR?
c. If more than one variation of the reported PROM exists, has a specific version of the PROM been distinctly defined when reported in the SR?

2. Accuracy
    a. Has the PROM reported in the SR been used at all in the referenced study?
    b. If a PROM reported in the SR has been used in the referenced study, was it the correct PROM that was reported?
    c. If the study provided evidence of self-reported adherence data, was the PROM used to collect the data declared?

Similarly to the validity assessment, these data were synthesised as part of a quantitative assessment to produce a percentage value that reflected the proportion of PROMs that met the minimum threshold for the reporting framework over the total number of eligible PROMs reported within each SR.

2.2.3.4 Bibliometric Assessment Criteria

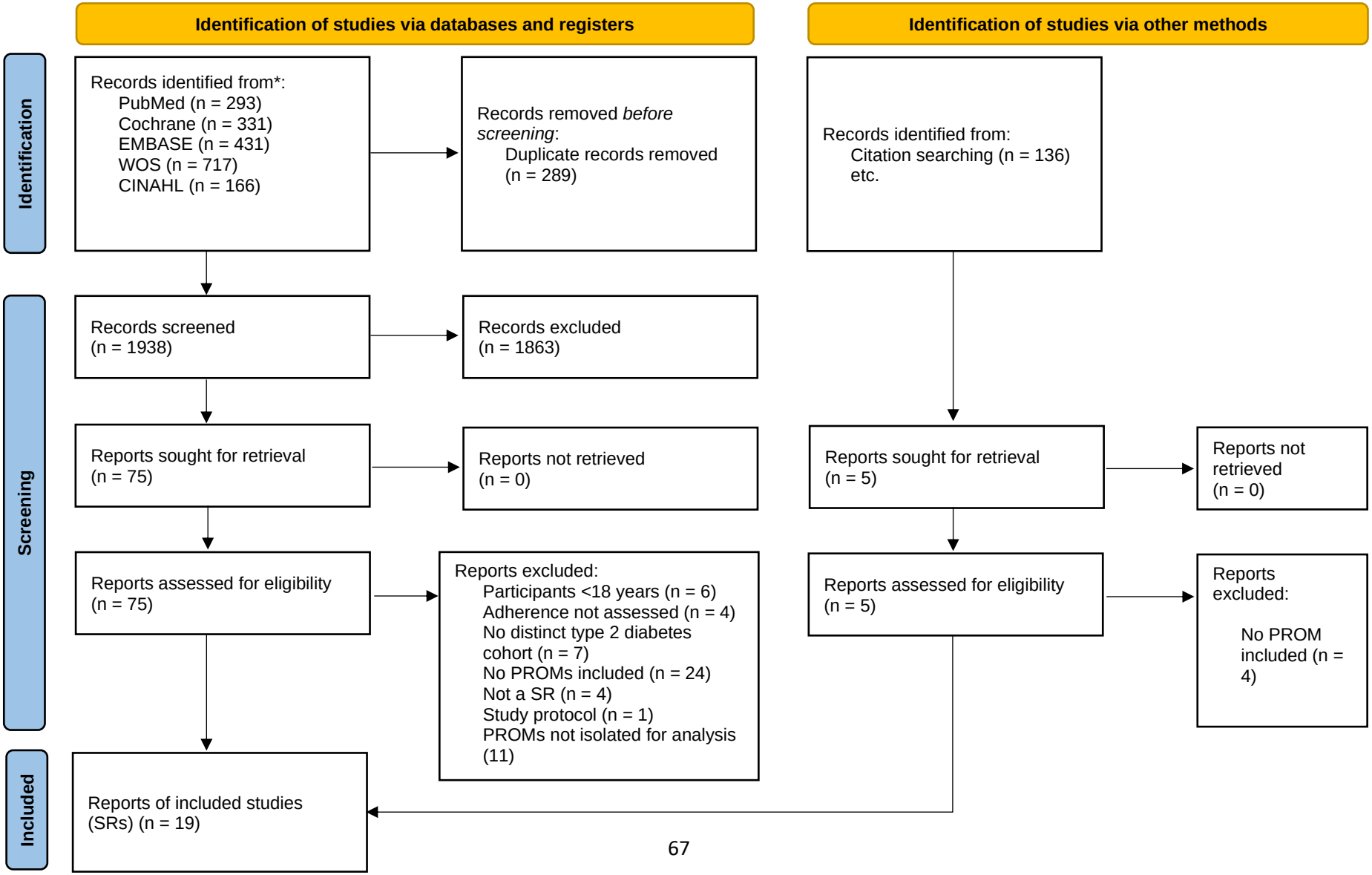
The SCImago Journal database was used to synthesise and collate quartile rankings for each SR included as part of the analysis. Non-parametric correlations were assessed using Spearman's Rho to explore any associations between impact factor and the prevalence of validity or reporting issues. A non-parametric correlation model was selected for the analysis based on the small sample size and heterogeneity of the data. Values of $p<0.05$ were considered significant.

2.3 Results

2.3.1 Preliminary Screening Summary Results

Prior to the initial title/abstract screening, 289 duplicates were removed to provide a total of 1938 eligible records. The screening resulted in the further removal of 1863 records prior to full-text screening (n=75). Screening of individual references for the included records (n=75) identified an additional five SRs for inclusion in the full-text screening phase (n=80). From the full-text screening, a total of 19 SRs were identified as eligible for inclusion in the full systematic analysis. Figure 2.2 provides a breakdown of the PRISMA diagram screening process, including details of reasons for exclusion.

Figure 2.2 – PRISMA 2020 Flow Diagram



2.3.2 Post-Screening Summary Results

A total of 19 SRs were included in the review. Across all SRs, the dates of publication for included studies covered a 30-year scope from 1990-2020. Table 2.3 describes the qualitative characteristics of the included SRs, such as primary/secondary outcomes, the type of T2D medicines reported, as well as the range of languages used to report the studies included within each respective SR. While the SRs covered a wide range of objectives, the outcomes could be aggregated into two major groups that included SRs examining factors that impact MA and related outcomes (n=6/19, 31.6%) and those assessing the impact of MA interventions (n=6/19, 31.6%). The remaining seven SRs were divided between evaluation of PROM psychometric properties (n=4/19, 21.1%) and describing MA rates in different populations (n=3/19, 15.8%). Each SR included patients prescribed OA agent, while only two SRs (10.5%) specifically excluded patients prescribed insulin.

A total of 1283 studies were reported within the 19 SRs, of which 241 were identified as eligible for analysis post-screening (Table 2.4). While 241 studies met the inclusion criteria for both the validity and taxonomy analyses, not all studies provided sufficient data for individual PROM analysis as part of the assessment frameworks designed for this review. Furthermore, several studies implemented more than one PROM as part of their reporting, hence the number of studies and overall number of reported PROMs are incongruent. In total, 247 eligible instances of PROM reporting were identified. The number of reported eligible PROMs was reduced when excluding duplicates through consolidation of data collated across all included SRs. A final list of 104 unique PROMs was produced. PROMs could be included more than once if they had a distinct and validated language adaptation.

Table 2.3 – Qualitative Characteristics of Included SRs

SR Number	Primary Outcome(s)	Secondary Outcome(s) (if defined)	Medicines Included	Language(s) of included studies
1	Prevalence of adherence (%)	Factors associated with MA behaviours	OA +/- insulin	English
2	Risk factors associated with non-adherence, interventions that improve adherence and of non-adherence on glycaemia		OA +/- insulin	English
3	Psychometric properties and validity of MMAS-8		OA +/- insulin	English
4	Assess relationship between PROs and economic outcomes		OA +/- insulin	English, Spanish, French, Italian
5	Evidence of barriers to MA, interventions to improve MA (focus on educators and self-care)		OA +/- insulin	English
6	Rates and factors affecting MA in MENA region		OA +/- insulin	No limitations
7	Evaluate the impact of general medication beliefs (via BeMQ) on MA		OA +/- insulin	English
8	Evaluate effectiveness of pharmacist interventions on adherence for OA		OA	No limitations
9	Identify MA methods for OA +/- insulin	Identify specific methods for assessing insulin regimen MA	OA +/- insulin	Not defined
10	Examine association between self-efficacy and diabetes self-management in middle-aged and older adults	Does the association apply across races and ethnicities	OA +/- insulin	Not defined - US reported studies hence assumed English only
11	Identify interventions to improve medication adherence in T2DM and their efficacy	Identify areas for future research based on the review outcomes	OA +/- insulin	English
12	Identify the measurement properties of PROMs MA in patients at risk for metabolic syndrome		OA +/- insulin	English
13	Evaluate interventions on medication adherence on DM in developing countries		OA +/- insulin	Not defined
14	Describe pharmacist interventions to improve adherence to OA medicines	Identifying the role of health behaviour theory in the development of interventions	OA	No limitations
15	Evaluate effectiveness of pharmacists' interventions on clinical outcomes and prevention of complications in diabetes mellitus		OA +/- insulin	English
16	To examine the relationship between adherence and glycaemic control and the effect of the measurement type on this relationship		OA +/- insulin	English
17	Summarise evidence of medication adherence and associated factors in LMIC		OA +/- insulin	Not defined
18	Summarise the psychometric properties of PROMs for MA	Assess the quality of the evidence	OA +/- insulin	English
19	Identify psychometric properties of PROMs validated for Type 2 Diabetes		OA +/- insulin	English

Abbreviations: OA, oral antiglycaemics; MENA, Middle East and North Africa; T2DM; DM, diabetes mellitus; LMIC, low- and middle-income countries

Table 2.4 – Quantitative Characteristics of Included SRs

SR No.	Title	Search period	Publication Year	Number of included studies	No. of T2DM PROM studies	No. of MA PROMs
5	Medication taking and diabetes: a SR of the literature[226]	1990-2007	2007	36	1	1
4	A SR of patient-reported and economic outcomes: value to stakeholders in the decision-making process in patients with type 2 diabetes mellitus[225]	1996-2010	2011	185	7	7
14	SR of pharmacist interventions to improve adherence to oral antidiabetic medications in people with type 2 diabetes[235]	DO-2011	2012	8	2	2
8	Improving the adherence of type 2 diabetes mellitus patients with pharmacy care: a SR of randomized controlled trials[229]	DO-2013	2014	6	4	3
9	A systematic literature review of methodologies used to assess medication adherence in patients with diabetes[230]	2007-2013	2014	59	15	14
11	Effective interventions to improve medication adherence in Type 2 diabetes: a SR[232]	2000-2013	2014	27	12	11
16	The association between the measurement of adherence to anti-diabetes medicine and the HbA_{1c}[237]	DO-2013	2014	23	4	6
1	Adherence to diabetes medication: a SR[222]	2004-2013	2015	27	18	19
2	Medication Adherence with Diabetes Medication: A SR of the Literature[223]	2007-2014	2016	98	31	32
12	Evaluation of the Measurement Properties of Self-reported Medication Adherence Instruments Among People at Risk for Metabolic Syndrome: A SR[233]	DO-2015	2016	32	11	13
6	Factors associated with medication adherence among patients with diabetes in the Middle East and North Africa region: A systematic mixed studies review[227]	Database origin (DO) - 2016	2017	30	14	11
3	Accuracy of a screening tool for medication adherence: A SR and meta-analysis of the Morisky Medication Adherence Scale-8[224]	2008-2015	2017	28	9	4
15	A Review of Pharmacist-led Interventions on Diabetes Outcomes: An Observational Analysis to Explore Diabetes Care Opportunities for Pharmacists[236]	2012-2018	2019	25	5	5
18	Measurement Properties of Existing Patient-Reported Outcome Measures on Medication Adherence: SR[173]	DO-2019	2020	214	35	36
7	The Consequences of General Medication Beliefs Measured by the Beliefs about Medicine Questionnaire on Medication Adherence: A SR[228]	1999-2019	2020	11	5	4
10	Self-Efficacy and Diabetes Self-Management in Middle-Aged and Older Adults in the United States: A SR[231]	1990-2018	2020	11	5	7
13	Medication adherence among diabetic patients in developing countries: Review of studies[234]	2000-2018	2020	57	16	20
17	A SR and meta-analysis of non-adherence to anti-diabetic medication: Evidence from low- and middle-income countries[238]	2000-2019	2020	43	26	31
19	Measurement Properties of Patient-Reported Outcome Measures for Diabetes: SR[239]	DO-2020	2021	363	21	21
Total				1283	241	247[a]

Notes: [a]After removal of duplicates, a total of 104 unique PROMs were identified

2.3.3 Summary of Identified PROMs

Of the 104 unique PROMs identified during the analysis (Table 2.5), the MMAS-4 was the most widely used accounting for roughly 14% (n=35/247, 14.2%) of all eligible instances of PROM reporting in individual studies. Furthermore, both the MMAS-4 and the longer 8-item adaptation, MMAS-8, were the PROMs with the highest number of translations identified during the analysis with 17 confirmed valid translations for both versions, respectively. In total, the PROMs included in the review represented >30 different languages reflecting PROMs suitably developed or adapted for populations in the Americas, Europe, Asia, and Africa. Middle Eastern language adaptations were some of the most common, including Arabic and Farsi (Persian) translations for >3 PROMs.

Table 2.5 – Associated PROM Translations & Adaptations

PROM	Adaptations
Adherence to Refills and Medication Scale (ARMS)	ARMS-7-Turkish, ARMS-12, ARMS-D, ARMS-K
Adherence Starts with Knowledge (ASK-12)	ASK-20
Brief Medication Questionnaire (BrMQ)	BrMQ-Thai, Modified-BrMQ
Cost-related Non-adherence (CRN)	CRN-Spanish, CRN-Vietnamese
Demirtas	Demirtas-Turkish
General Medication Adherence Scale (GMAS)	GMAS-Urdu
Medication Adherence Rating Scale (MARS-5)	MARS-5-Arabic, MARS-5-Dutch, MARS-5-Portugese, MARS-10-Farsi, MARS-5-Chinese, MARS-10-Persian
Medication Treatment Adherence (MTA-Portuguese)	MTA-Insulin, MTA-OAD, MTA-Arabic
Morisky Medication Adherence Scale (MMAS-4[a])	MMAS-4-Ahmaric, MMAS-4-Arabic, MMAS-4-Chinese, MMAS-4-Afan Oromo, MMAS-4-Ewe, MMAS-4-French, MMAS-4-Ga, MMAS-4-German, MMAS-4-Indonesian, MMAS-4-Korean, MMAS-4-Khmer, MMAS-4-Maralayam, MMAS-4-Portugese, MMAS-4-Spanish, MMAS-4-Thai, MMAS-4-Turkish, MMAS-4-Twi
MMAS-8	MIAS, MALMAS, MMAS-8 (Ethiopia), MMAS-8 (Tanzania), MMAS-8-Afan-Oromo, MMAS-8-Ahmaric, MMAS-8-Arabic, MMAS-8-Chinese, MMAS-8-Ewe, MMAS-8-Farsi, MMAS-8-French. MMAS-8-Indonesian, MMAS-8-Kannada, MMAS-8-Korean, MMAS-8-Malay, MMAS-8-Mandarin, MMAS-8-Persian, MMAS-8-Spanish, MMAS-8-Tamil, MMAS-8-Thai, MMAS-8-Tigrigna
Summary of Diabetes Self-care Activities (SDSCA-Revised)	SDSCA-MS, SDSCA-5-Item, SDSCA-11-Persian, SDSCA-Revised-Ahmaric, SDSCA-Revised-Hindi, SDSCA-Revised-Spanish, SDSCA-Revised-Turkish
Self-care Inventory (SCI-Revised)	SCI-Catalan, SCI-Spanish, SCI-Urdu
Voils-English	Voils-Chinese, Voils-Malay

Notes:[a]MMAS-4 and MMAS-8 were divided into subcategories to provide a clearer representation of the large number of respective adaptations captured within this review

Abbreviations: ARMS, Adherence to refills and medication scale; ARMS-7-Turkish, Adherence to refills and medication scale 7-item Turkish version; ARMS-12, Adherence to refills and medication scale 12-item; ARMS-D, Adherence to refills and medication scale diabetes version; ARMS-K, Adherence to refills and medication scale Korean version; ASK-12, adherence starts with knowledge 12-item; ASK-20, adherence starts with knowledge 20-item; BrMQ, brief medicines questionnaire; BrMQ-Thai, brief medicines questionnaire Thai version; modified- BrMQ, modified brief medicines questionnaire; ; CRN, cost-related non-adherence; CRN-Spanish, cost-related non-Demirtas-Turkish, Demirtas questionnaire Turkish version; GMAS-English, general adherence to medication scale English version; MARS-5, medication adherence rating scale 5-item; MTA-Arabic, measurement of treatment adherence Arabic version; MTA-OAD, measurement of adherence to drug therapy in oral antidiabetics; MTA-Insulin, measurement of adherence to drug therapy in insulin; MMAS-4, Morisky medication adherence scale 4-item; MMAS-8; Morisky medication adherence scale 8-item; MALMAS, Malaysian medication adherence scale; MIAS, Morisky medication adherence scale adapted to specify insulin adherence; SDSCA-Revised, summary of diabetes self-care activities revised version; SDSCA-MS, summary of diabetes self-care activities medicines subscale; SCI-R, self-care inventory revised; Voils-English, Voils questionnaire English version;

2.3.4 Validity Assessment

Of those SRs published after 2010 (n=18), only three (16.7%) implemented the COSMIN checklist and just over a fifth of included SRs (n=4/19, 21.1%) reported PROM validity criteria as outlined in section 2.2.3.2 (Figure 2.3). Roughly two-thirds (n=12/19, 63.2%) had reported non-validated PROMs (Table 2.6). At an individual study level, just under a quarter

of all reported PROMs (n=58/247, 23.5%) failed to provide adequate evidence of validity as defined by the framework in this review. The overwhelming majority of cases (n=47/58, 81.0%) were attributed to a lack of evidence for validity of translated PROMs. When assessing this, if the study had referenced an alternative study for their PROM, the reference study was examined to assess if the minimum validity evidence, as outlined in this review, had been demonstrated for that specific PROM. The same methodology was applied for translated PROMs to check for cross-cultural validation. PROMs that had only been validated in other target conditions were used in seven studies (n=7/58, 12.1%). The remaining four studies (n=4/58, 6.9%) that failed to reach the minimum threshold for validity based on the assessment criteria provided no evidence of target language for the study population whilst using a PROM that did not have a translated adaptation relevant to that population, e.g., MMAS-8 (originally designed in English) was used amongst a population in Ethiopia, however no evidence of translation or cohort competency in English was defined to assess the validity of the PROM.

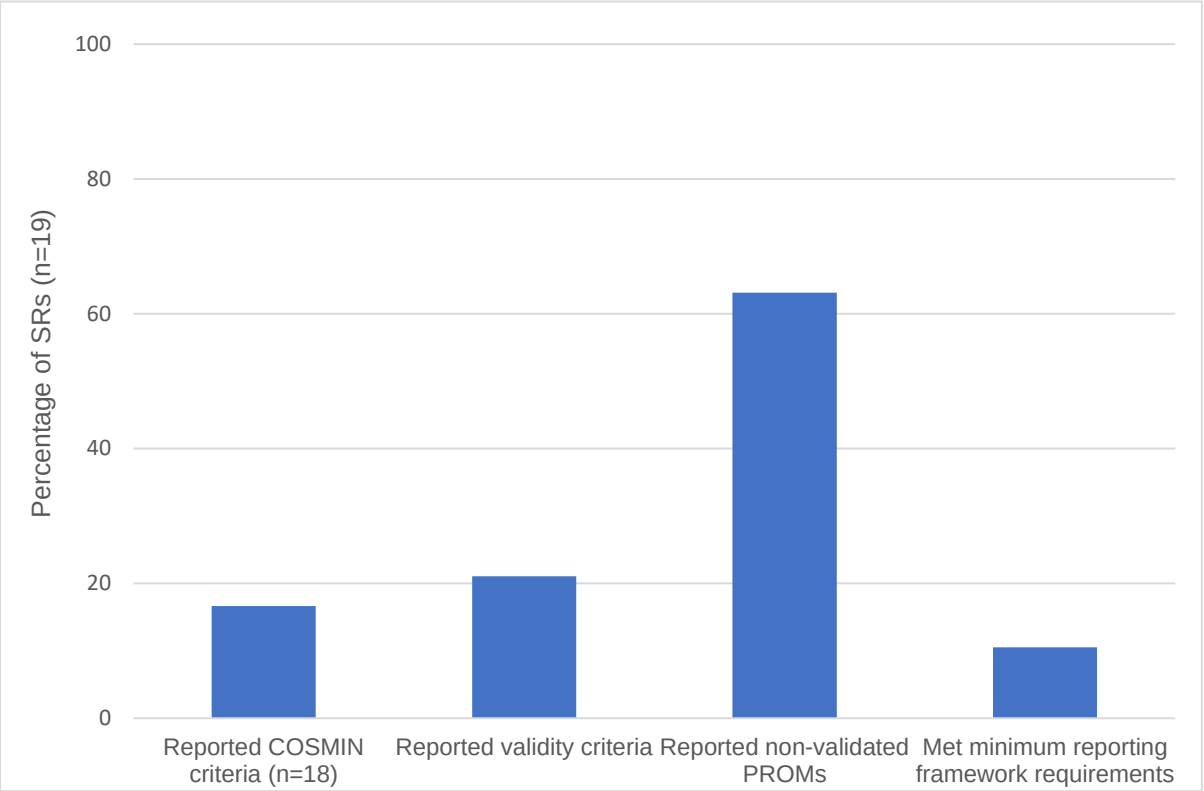


Figure 2.3 – SR Assessment Criteria

Notes: The COSMIN criteria were introduced in 2010, which excluded one SR from the analysis due to its publication prior to 2010, hence n = 18 for this sample. A total sample of n = 19 was used to assess the other criteria included in this figure.

Table 2.6 – Validity Assessment of PROMs

SR No.	No. studies (n)	No. PROMs (n)	Identified PROMs (n)	PROMs without validity (n, %)	Exclusion Reasons (n)
1	18	19	MMAS-4 (9), MMAS-4-German (1)[a], MMAS-4-Korean (1), MMAS-8 (1), MARS-10-Persian (1)[a], MMAS-8 Arabic (1), MTA-Arabic (1)[a], SDSCA-MS (1), Girerd Questionnaire (1)[b], MCQ (1)[c], CRN (1)	5 (26.3)	Language (3) Target condition (1) Language not defined (1)
2	31	32	MMAS-8-Malay (2), MMAS-4-German (1)[a], MMAS-8-Arabic (2), CRN (1), CRN-Spanish (1)[a], CRN-Vietnamese (1)[a], MMAS-4-Spanish (2), MMAS-4 (9), MMAS-8 (2), MARS-5-Dutch (2)[a], BrMQ (2), SDSCA-5 (1), MARS-10-Persian (1)[a], MARS-5 (2), ARMS-12 (1), MMAS-4-French (1)[a], MMAS-8-Persian (1)	7 (21.9)	Language (7)
3	9	4	MMAS-8-Arabic (1), MMAS-8-French (1), MMAS-8-Ewe (1), MMAS-8 (1),	0	
4	7	7	MMAS-4 (3), BrMQ (1), MARS-5 (1), DSAS-Chinese (1), SDSCA-Revised (1)	0	
5	1	1	MMAS-4 (1)	0	
6	14	11	MTA-Arabic (2)[a], MMAS-8-Arabic (4), MMAS-4-Arabic (1), MMAS-8-Thai (1), SDSCA-11-Persian (1), MARS-10-Farsi (2)[a]	4 (36.4)	Language (4)
7	5	4	MARS-5-Chinese (1), MARS-5-Portuguese (1), MMAS-8-Arabic (1), MARS-5-Arabic (1)	0	
8	4	3	BrMQ-Kannada (1)[a], MMAS-4-Portuguese (1)[a], 2-item-Haynes (1)[b]	3 (100.0)	Language (2) Target condition (1)
9	15	14	MMAS-8 (2), SDSCA-MS (1), MMAS-4 (3), MARS-5 (2), SDSCA-Revised (2), MMAS-8-Spanish (1)[a], MTA-Portuguese (1), BrMQ (1), RAM Scale (1)	1 (7.1)	Language (1)
10	5	7	SDSCA-Revised (2), SDSCA-Revised-Spanish (2)[a], Hill-Bone Compliance Scale (1)[b], modified-BrMQ (1)[b], MMAS-8 (1)	4 (57.1)	Language (2) Target condition (2)
11	12	11	MMAS-8 (2), MMAS-8-Spanish (1)[a], MARS-5 (2), Hill-Bone Compliance Scale (2)[b], MMAS-4-Arabic (1), BrMQ (1), MMAS-8-Persian (1), Edwards-Regimen Adherence Score (1)	3 (27.3)	Language (1) Target condition (2)
12	11	13	ARMS (1), ARMS-D (1), ASK-12 (1), ASK-20 (3), MMAS-4 (2), MMAS-4-Chinese (1), MMAS-8-Malay (1), MMAS-8-Korean (1), MMAS-8-Thai (1), VAS (1),	0	
13	16	20	MMAS-8 (Ethiopia) (2)[C], MMAS-8 (4), MMAS-8 (Tanzania) (1)[c], MTA (1)[a], SCI-Urdu (1), MMAS-8-Arabic (2), MMAS-4-Ga (1)[a], MMAS-4-Twi (1)[a], MMAS-4-Ewe (1)[a], MTA-Portuguese (1), MMAS-8-Chinese (1), MMAS-8-Amharic (2)[a], MMAS-8-Afan Oromo (2)[a]	11 (55.0)	Language not defined (3) Language (8)
14	2	2	MMAS-4-Spanish (1)[a], BrMQ (1)	1 (50.0)	Language (1)
15	5	5	MMAS-8-Malay (3), MMAS-4-Turkish (1)[a], MMAS-8-Farsi (1)	1 (20.0)	Language (1)
16	4	6	MMAS-8-Malay (1), MMAS-8 (1), MMAS-4 (3), MMAS-4-Chinese (1)	0	
17	26	31	MMAS-4-Afan Oromo (1)[a], MMAS-8-Kannada (1)[a], MMAS-4-Khmer (1), MMAS-8-Tamil (1)[a], MMAS-8-Tigrigna (1)[a], MTA-Arabic (1)[a], MMAS-8-Amharic (4)[a], SDSCA-Revised-Amharic (2), MMAS-8 (3), MMAS-8-Indonesian (1), MMAS-4-Amharic (5)[a], MMAS-8-Arabic (3), MCQ (1), SDSCA-Revised-Hindi (1)[a], MMAS-4-Malayam (1)[a], MMAS-8-Malay (1), MMAS-8-Mandarin (1), MMAS-4-Arabic (1), MMAS-8-Afan Oromo (1)[a]	17 (54.8)	Language (17)
18	35	36	AACTG (1)[b], ARMS (1), ARMS-7-Turkish (1), ASK-12 (1), ASK-20 (2), BrMQ-Thai (1), GATM-French (1), GMAS-Urdu (1), GMAS-English (2), IADMAS-Arabic (1), MAS-12-Japanese (1), MMAS-4 (2), MMAS-4-Indonesian (1), MMAS-4-Chinese (1), MMAS-4-French (1), MMAS-8-Arabic (1), MMAS-8 (1), MMAS-8-Persian (1), MMAS-8-Thai (1), MMAS-8-French (2), MIAS-8 (1), MNPS (1), PT/PP (1), SCI-Urdu (1), SCI-Spanish (1), SCI-Catalan (1), SDSCA-MS (2), Voils-English (1), Voils-Chinese (1), Voils-Malay (1), Demirtas-Turkish (1)	1 (2.8)	Target condition (1)
19	21	21	SDSCA-Revised (1), SDSCA-Revised-Turkish (1), SCI-R (1), D-SMART-Spanish (1), V-DSMI (1), DSMB-O (1), SMP-T2D (1), Demirtas (1), MMAS-4-Thai (1), MMAS-4 (1), MMAS-4-Chinese (1), MMAS-8-Korean (1), MMAS-8-Chinese (1), MMAS-8-French (2), MMAS-4-Indonesian (1), MALMAS (1), MAT-OAD (1), MAT-Insulin (1), ARMS-K (1), GATM-French (1)	0	
Total	241	247		58	

Notes: [a]No evidence provided for validity of PROM in target language; [b]No evidence provided for validity of PROM in type 2 diabetes cohort; [c]Language not defined – Language of original PROM is discordant from expected language of patient cohort

2.3.5 Reporting Assessment

When assessed against the reporting framework designed specifically for this review, only two SRs (n=2/19, 10.5) provided evidence to demonstrate that the minimum standard for PROM reporting was met for every study included in their respective review (Figure 2.3). Less than half (n=114/241, 47.3%) of the included studies were identified as not meeting the minimum standard for reporting (Table 2.7). Roughly three-quarters (n=84/114, 73.7%) of identified issues were the result of taxonomical inconsistencies relating to the target language or distinction of PROM adaptations when assessed against the reporting framework. Additionally, it was identified that there was an incongruence in the PROM used in the study and reported in the SR (n=11/114, 9.6%). For example, at least three SRs reported the use of the SDSCA as a measure of MA for studies identified in their reviews, however on closer examination of the source literature, the MA items of the SDSCA had been omitted in each study and alternative PROMs had been implemented, such as the BrMQ. Furthermore, a total of seven studies (n=7/114, 6.1%) were identified with both a suitable methodology and evidence to report the use of a validated PROM yet the SR failed to declare the PROM within the manuscript. In fact, a common term used in lieu of identifying a specific PROM was "self-report". This terminology was used to declare that a measure of MA had been implemented with a specific self-report method, but without ascribing this measure to a specific PROM. An example of this includes a SR that described "self-reported MA", when in fact the MMAS-4 had been implemented but not declared.[226]

Table 2.7 - Reporting Assessment of PROMs

SR Number	No. studies (n)	Studies below reporting standard (n,%)	Exclusion Reasons (n)
1	18	3 (16.7)	Taxonomy[a] (3)
2	31	19 (61.3)	Taxonomy (17) Tool reported not used in study (1) Incorrect tool reported (1)
3	9	6 (66.7)	Described but not referenced (6)
4	7	5 (71.4)	Taxonomy (5)
5	1	1 (100.0)	PROM not declared (1)
6	14	11 (78.6)	Taxonomy (8) Described but not referenced (1) Incorrect tool reported (1) Tool reported not used in study (1)
7	5	5 (80.0)	Taxonomy (3) Described but not referenced (2)
8	4	2 (50.0)	PROM not declared (2)
9	15	7 (46.7)	Taxonomy (6) Incorrect tool reported (1)
10	5	2 (40.0)	Incorrect tool reported (1) Taxonomy (1)
11	12	8 (66.7)	Taxonomy (6) Incorrect tool reported (1) Tool reported not used in the study (1)
12	11	0	
13	16	8 (50.0)	Incorrect tool reported (2) Taxonomy (6)
14	2	2 (100.0)	Taxonomy (2)
15	5	2 (40.0)	PROM not declared (2)
16	4	3 (75.0)	Taxonomy (3)
17	26	28 (107.7)[b]	Taxonomy (24) Incorrect tool reported (2) PROM not declared (2)
18	35	2 (5.7)	Incorrect tool reported (2)
19	21	0	
Total	241	114	

Notes:[a]Taxonomical issues included cases where either the target language was not defined if different from the original PRO, or if no distinction had been made between adaptations of a PROM; [b]Some studies reported >1 eligible PROM and hence could potentially exceed 100.0%

2.3.6 Bibliometric Assessment

Quartile data for journal publication quality were derived from the SCImago database. In total, 17 (89.5%) of SRs included in the review were identified with a SCImago journal ranking with a range from 1-3. A higher ranking is indicative of a lower journal impact factor. A significant moderate correlation was observed (r=0.44, p=0.04) when comparing the SRs with the highest proportion of PROMs reported without adequate validity and the impact factor of journals where the SR were reported. A greater prevalence of non-valid reporting was positively associated with a higher quartile ranking or lower journal impact factor. However, the association observed between the quartile ranking and the prevalence of SRs with reporting issues was not significant (p>0.05).

2.4 Discussion

This review took a unique approach to demonstrate the scope, validity, and reporting of PROMs of MA among individuals living with T2D. More specifically, broad inclusion criteria were developed to allow for a wide range of SRs to be identified during the screening phase. This resulted in the collation of SRs reporting studies across a 30-year span of literature. Furthermore, while only SRs published in English were included, individual studies reporting PROMs in different target languages were analysed leading to the representation of PROMs in 30 unique languages and dialects. Interestingly, this approach led to more diverse representation of research from low- and middle-income countries, which are often disaggregated for specific studies and as a result, are underrepresented in health research.[240] This systematic analysis therefore successfully provides a historical and global commentary on PROM research in relation to MA in the sample population.

2.4.1 Classification & Validity of PROMs

Several methodologies for the reporting and implementation of PROMs have been described in the literature. Most notably, these include the COSMIN criteria,[186] as well as specific guidelines designed for PROMs within clinical (FDA PROM Checklist)[241] and randomised (CONSORT (Consolidated Standards of Reporting Trials (CONSORT) PRO)[242] trials, all of which provide a specific benefit through standardisation of methodologies and reporting across the literature.[243] Somewhat unsurprisingly, those SRs[173,244] that utilised the COSMIN criteria reported the least issues in relation to validity and/or reporting of PROMs when compared against the assessment framework designed for this review.

Arguably, Kwan *et al*[173] (SR 18) have provided the most comprehensive SR to date, identifying 31 unique PROMs of MA in T2D as part of a total of 121 unique PROMs of MA for all clinical conditions identified in their review. In contrast to this review which identified 104 PROMs specifically developed for individuals living with T2D, Kwan *et al*[173] did not classify language adaptations of PROMs as separate tools; although it should be noted that languages for each PROM were documented in the appendix. The COSMIN criteria describe 'culturally different population[s]' as "different ethnicity or language groups…but also other groups such as different gender or age groups…", however this particular aspect of classification is not discussed in further detail. While perhaps there is no currently agreed 'gold standard' approach to PROM classification in terms of language or dialect, the results of this review highlighted that the greatest proportion (81.0%) of individual studies identified with concerns relating to validity, were those reporting translated adaptations. This may be in part due to an assumption of construct equivalence between translations. However, as Hawkins *et al*[245] demonstrate in their SR of the impact of linguistics on construct equivalence, this assumption can often be incorrect due to translation errors, specifically

where the use of complex phrases, words, semantics, and grammar may affect the forward translation of PROMs.

The assumption of construct equivalence between translations was identified in almost two-thirds of SRs; this may directly jeopardise the reliability and/or validity of the PROM. Hawkins *et al*[245] also highlight that the confirmation of equivalence or invariance should be assessed post-translation through the implementation of statistical methods for CCA.[246] Although this recommendation is clear, its implementation may be limited given that as of 2015, no clear consensus between guidelines for CCA had been identified, as reported by Epstein *et al*.[247] Despite this, the authors emphasise that additional evidence for CCA and the development of a consensus is required, particularly methodological strategies for translation and assessment of psychometric properties.[247] Hence, this SR highlights the potential impact and importance of describing and delineating between translated adaptations of PROMs in primary and secondary literature, such as SRs. This approach may help to improve the transparency of CCA, or lack thereof, with a view to identify potential validity issue associated with PROM reporting.

2.4.2 Reporting of PROMs

Beyond commonly reported determinants of validity e.g., CCA, this review looked to examine issues specifically relating to taxonomy and inaccurate interpretation of PROMs. The provision of taxonomy for PROMs enables researchers to take an organised approach to evaluating what each measure does, as well as identify gaps and overlaps between different models – this may be of particular benefit when comparing tools within the same area of research or implementation.[248] The results of this review revealed a need for clearer guidance and standardisation of PROM reporting, despite the availability of tools such as the COSMIN criteria.

One of the most identified issues in the analysis is related to the misinterpretation of the SDSCA. Toobert and Glasgow[219] developed the original tool in 1994. A later review of SDSCA literature conducted in 2000 saw a revision to the tool, which recommend the removal of items pertaining to MA as a result of significantly reported ceiling effects.[249] Despite the removal of MA items, the reference to the revised scale, as a measure of MA, was cited across several SRs.[173,222,223,225,227,230,231,233,238] Most SRs reported the SDSCA generically, however various iterations of the tool had been used in the studies reported including a single medication subscale (SDSCA-MS), a 5-item adaptation (SDSCA-5), as well as the original tool (SDSCA) and revised version (SDSCA-Revised). In addition, the issues raised by Hawkins *et al*[245] regarding the failure to conduct appropriate CCA post-translation were also prevalent among several of the language adaptations of the SDSCA model. Moreover, on three occasions, the SDSCA was reported as the PROM used to examine MA, however upon further examination of the primary literature (the studies included within each respective SR), it was found that the MA items had been omitted.[223,231,232] This scenario presents a few issues. In accordance with the COSMIN criteria, individual subscales are to be treated as independent PROMs given that they measure defined constructs with discrete psychometric properties. Studies that therefore implement adaptations and interpret their results (often devoid of reliability or validity data) without due care may fail to address the high variability associated with PROM outputs.[175,176]

There is a considerable risk that without the use of standardised approaches to either report or identify PROMs, future research, specifically reviews, may fail to collate, and synthesise data derived for a specific measure(s). In fact, two notable PROMs were completely omitted across all included SRs, including the German version of the MARS (MARS-Deutsch)[250] and the German adaptation of the SDSCA (SDSCA-G).[251] Both studies were published within the

last decade and could therefore be considered more recent publications when compared with the three-decade scope of reporting captured within this review. Furthermore, each study provides evidence of psychometric properties for their given PROM and highlights distinct sample populations for a cohort of individuals living with T2D when samples with more than one chronic condition were recruited. Both studies would have therefore met the inclusion criteria for this systematic analysis if included in the SRs.

2.4.3 COSMIN Implementation, Bibliometrics, & Real-World Risks

Collating and evaluating research on TMB, from which PROMs are derived, has previously been subject to limitations due to the qualitative and subjective nature of their reporting and interpretation.[151] Unsurprisingly, this limitation also extends to the assessment of PROM related literature, particularly given the breadth and diversity of reporting as highlighted by Wee *et al*.[244] One might assume given this limitation that authors would opt for the implementation of standardised methodologies, however only three of the 18 SRs published after 2010 included the COSMIN criteria.[186]

While not all SRs focused on the measurement outcomes of PROMs, a substantial proportion exhibited validity and reporting concerns, with a noticeable association between quartile ranking and validity issues. Although bibliometric indicators like quartile ranking should not be relied upon as standalone measures of research quality, it is acknowledged that the moderate correlation (>0.4)[252] discovered using Spearman's Rho is noteworthy in terms of validity reporting within this systematic analysis and warrants further exploration in future research.[253] An over-reliance on PROMs and their reporting without suitable scrutiny of their validity, cross-cultural applicability, and implementation has already demonstrated potentially negative real-world effects. Krogsgaard and Hansen[254] highlight the risk of irresponsible healthcare recommendations becoming increasingly common due to the misuse

of PROMs. The authors discuss several clinical studies on musculoskeletal conditions, which increasingly use PROMs as primary outcomes – these results may ultimately have an impact on real-world clinical practice. As an example, in 2010, the New England Journal of Medicine (NEJM) published a randomised study on the treatment of acute anterior cruciate ligament (ACL) rupture, with the primary outcome being Knee injury and Osteoarthritis Outcome Score 4 (KOOS4).[255] KOOS (the original PROM) has previously been identified as invalid for patients with ACL using Rasch analysis, furthermore the validity of KOOS4 has not been documented. As a result, even the KOOS homepage advises against its use. This case highlights that even prestigious publications in terms of quartile ranking and bibliometrics are not exempt from the concerns raised by the review in terms of validity and reporting of PROMs. Though, one might question whether the responsibility sits more with authors, reviewers, or equally across both parties in addressing these concerns.

It is worth emphasising that several of the problems identified in this review could be addressed in part by better implementation of the COSMIN criteria and related guidelines, which provide a standardised framework for evaluating and reporting PROM validity that can be used by authors and/or reviewers when conducting and assessing research. However, it is also important to recognise that these frameworks are not without their own limitations. For example, Kwok *et al*[243] identified an incredibly significant time cost amongst a group of post-graduate level researchers to become familiar with, and then implement, the COSMIN tool in their case-based example study. The authors highlight specifically that within clinical settings, neither the time nor academic experience necessary to conduct this work would be suitable and hence may limit the use of such frameworks within clinical practice and/or other areas where abbreviated methods may be more applicable.

To this extent, this review has developed three key recommendations (Table 2.8) as part of a novel framework based on the results of the systematic analysis that may be beneficial to PROM research at both the individual study and SR level, while also applicable to authors, reviewers, and those with limited time, resources, or experience to implement larger frameworks, such as the COSMIN criteria.

Table 2.8 - Recommended Framework Items for PROM Research

Number	Recommendation
1	Adapted translations of PROMs should be distinctly categorized from the original PROM and reported as such. Construct equivalence should not be assumed unless a clear methodology for translation is described, and relevant post-translation psychometric properties are reported. If the PROM was translated in a previous study, the validity of the methods used to translate the PROM should be assessed using these criteria prior to citation of the study.
2	Adaptations of PROMs that affect subscales and/or items should be distinctly categorised from the original PROM and reported as such. Relevant psychometric properties of the adaptation should be reported unless the analyses were conducted in a previous study, whereby these methods should be assessed to determine the validity of the adaptation using these criteria prior to citation of the study.
3	Where relevant and available, reference to an appropriate guideline for reporting or determining psychometric properties of PROMs, such as the COSMIN criteria, should be clearly cited in the study or SR. If no relevant guideline or framework is followed, a statement to justify exclusion may be appropriate to support the interpretations of the study/SR results and their reliability for external audiences

2.4.4 Limitations

This review's scope may be restricted as it excluded non-English SRs. Additionally, the baseline criteria for validity reporting were relatively lenient, suggesting that more validity concerns may have arisen with a stricter approach. This SR concentrated solely on PROMs that assess medicine-taking behaviour in the context of MA, without considering other factors that influence MA behaviour, such as treatment satisfaction or beliefs about medication. Therefore, research should incorporate these types of PROMs in any future evaluation.

2.5 Conclusion

This systematic analysis offers extensive insights into the current landscape of PROMs used for assessing MA in patients with T2D. It is hoped that researchers and reviewers may consult this review while assessing the suitability and implementation of PROMs in future studies. Furthermore, this review may support the review of methodological issues highlighted in the analysis, which should be considered when developing study protocols related to PROMs.

To the author's knowledge, this SR is the first to adopt a granular approach to PROM classification based on language and scale adaptations. The review provided a centralised quantitative evaluation of translations and adaptations of widely used PROMs, such as the MMAS-4 and MMAS-8, with 17 translations identified for each adaptation, respectively. The systematic analysis also identified a high prevalence of issues related to PROM validity and reporting, primarily with respect to CCA. Hence, standardised methodologies are recommended to assess and report PROM validity.

This review has also highlighted the underutilisation and limitations of larger PROM reporting and assessment frameworks within the literature. In response, a novel framework has been developed that provides three clear recommendations on the reporting and assessment of PROMs and related research that may be of particular benefit for researchers/clinicians with limited time, resources, and experience in using frameworks such as the COSMIN criteria. The significant relationship between journal quartile ranking and the number of observed validity issues among published studies is an additional notable finding that warrants further exploration with a larger sample to establish a conclusive correlation. Moreover, this is the first review to quantify and identify the poor uptake of the COSMIN criteria with respect to PROMs used in patients living with T2D. Future work should explore

PROMs that investigate other drivers of MA and alternative clinical conditions, such as COPD.

Chapter 3: SPUR: Psychometric properties of a patient-reported outcome measure of medication adherence in Type 2 Diabetes

3.1 Introduction

As outlined in Chapter 1, T2D is a chronic condition with health economic and clinical outcome implications at a global scale.[59] It is evident that MA is a critical element of optimal T2D management by helping to achieve glycaemic control, preventing disease-related complications and the risk of mortality, which ultimately results in improved HrQoL.[86] While MA is recognised as an important component of T2D management, particularly in relation to glycaemic control, poor MA is common among this population with less than 50% of individuals taking their medicines as prescribed.[256] In order to improve MA among people living with T2D, one must first understand patients' experiences and perspectives on medication use that ultimately impact their MA behaviour. PROMs may be useful tools to achieve this.

3.1.1 Challenges Associated with PROMs

Chapter 2 introduced several PROMs used for determining MA and related behaviour in T2D as well as their relevance in clinical practice e.g., associations with disease-related outcomes and glycaemic control.[210–212] However, despite these potential benefits, there are still challenges to the widespread adoption and appropriate use of PROMs in clinical practice such as:

- Poor evidence of content validity or reliability for newly developed PROMs that limit their utility in clinical settings.[206,207,257]
- Inconsistency in the reporting of PROMs and the taxonomy used to describe different models that may impede their selection or review by researchers/clinicians.[192,258]

- The availability of a large and qualitatively complex range of PROM studies, thus making it difficult to select an appropriate model for development, validation, and implementation in real-world settings.[151,244]

While these potential barriers persist, the findings of Chapter 2 also highlighted many PROMs with suitable evidence of reliability, broad cross-cultural validity, and a wide range of linguistic adaptations, with MMAS-4/8 being one of the most notable examples.[209,259] The lack of a 'gold-standard' PROM for measuring MA is commonly discussed in the literature.[260,261] Yet, given its notoriety, global applications, and adaptations since its inception in the 1980s, the MMAS is considered by some as a pseudo gold-standard model to measure MA.[262] However, even such a renowned model is not without limitation. As the name might suggest, the MMAS-8 contains eight items. These items specifically explore direct medication taking behaviour as well as barriers, including forgetfulness, and an individual's control of their health status as determinants of adherence.[172] One can immediately recognise that beliefs about medicines, a core component of MA behaviour and PROM development as discussed by Nguyen *et al*,[172] is omitted from this model. Hence, it is reasonable to question whether a PROM that fails to holistically address such a key driver of MA can reliably predict this outcome in all patients within real-world settings. Of course, this applies to all MA PROMs given that to date no holistic or gold-standard model has been developed or reported.

The need for a holistic approach to assessing MA is emphasised by Martin *et al.*[174] Even PROMs that measure the same drivers of MA behaviour in the same sample population have demonstrated significant differences in their results.[175,177,206] These disparities may be indicative of the complexity of capturing MA behaviour, inconsistent validity, interpretation, and reporting of some models and their results, or even a lack of consideration for external

factors such as the Hawthorne effect.[20,162–164] While the answer to these differences requires further investigation, it remains clear that a multi-faceted assessment of behavioural determinants may provide a clearer and more reliable picture of an individual's risk of non-adherence. With this hypothesis in mind, the SPUR model was developed as a holistic PROM of MA in patients living with chronic conditions. The design of SPUR will be discussed in more detail in the Methods section of this Chapter.

3.1.2 Validation of PROMs – Exploring the COSMIN Initiative & Limitations of PRO Frameworks

To ensure that the SPUR model could fully address the limitations identified in the previous section, it was critical that a suitable methodology was established to demonstrate the validity, reliability, and as a result, overall clinical utility of the model.

One methodology of interest was the COSMIN criteria. The initiative recognised poor uptake of standardised methodologies for the development and adaptation of PROMs (as outlined in Chapter 2). Hence, the COSMIN criteria outline a taxonomy developed from the initiative while providing definitions of nine measurement properties as well as agreed-upon standards for evaluating studies that examine measurement properties (Table 2.1). The criteria provide a useful framework from which to develop a validation protocol that can address each component of the study design checklist. However, in their 2018 paper, Hawkins *et al*[263] suggested that despite the availability and reporting of COSMIN and other PROM validity testing processes, such as the FDA guidance for industry[187] and International Society for Quality-of-Life Research (ISOQoL) minimum measurement standards,[264] testing theory and methodology are seldom implemented with a view to demonstrate on-going and accumulated evidence of validity. This may in part be due to several limitation such as their complexity and time taken to implement in real-world settings, particularly with reference to clinical

settings where appropriate experience with the methodology among clinicians/clinical researchers may be limited.[243] Moreover, while the COSMIN criteria outline guidance on study design and measurement properties for both unidimensional and multidimensional models, the latter are often more complex and it may therefore be difficult to apply the strict psychometric assessment framework. To address some of these limitations, particularly in situations where clinicians may struggle to understand or implement elements of the COSMIN criteria, such as assessing responsiveness, Angst[265] suggests a blended approach of traditional methods and those suggested by Mokkink *et al.*[186]

3.1.3 Rationale

It is evident that while a broad range of comprehensive resources exist that help to define standards for reporting measurement properties, there is no agreed gold standard approach for collectively demonstrating suitable psychometric properties of a novel PROM, clear guidance on clinical relevance and utility, or consensus on how best to capture iterative and accumulated evidence of validity. From a clinical perspective, MA for people living with T2D, among many other chronic conditions, has been identified as a large health economic and clinical outcome burden. PROMs can provide particularly critical information to support the clinician decision-making and the development of tailored interventions. Despite this, no holistic PROM of MA in T2D has been developed to date.

3.1.4 Aims & Objectives

This study aimed to develop and deliver a bespoke validation study for a multidimensional PROM (SPUR) of MA in patients living with T2D. The objectives are as follows:

- To evaluate the psychometric properties of SPUR in patients diagnosed with T2D from community and hospital settings

- To explore the associations between SPUR (adherence) and other socio-demographic/socio-clinical factors
- To compare SPUR as a multidimensional model to other PROMs validated in T2D

3.2 Methods

3.2.1 Synopsis

This study forms part of a larger set of international studies that have evaluated the SPUR model as a PROM of MA. The UK arm sought to provide early evidence of validity for SPUR in people living in the UK diagnosed with T2D. To achieve this, a three-tier study protocol conducted across two phases was developed that comprised the following:

Phase 1

1. Literature Review – A scoping review of the literature was conducted to identify 1) relevant protocols and/or studies that could be used to develop a bespoke framework for validation of the holistic SPUR model 2) suitable comparator PROMs that could be incorporated into the study to provide meaningful data that could be derived as evidence for construct/convergent validity of the SPUR model 3) objective measures of MA that could be used to demonstrate the evidence of concurrent validity for the SPUR model

Phase 2

2. Pilot Study – A mixed methods pilot study was designed and delivered that sought to determine the face and content validity of the English version of the SPUR model with people living with T2D. Furthermore, HCPs were recruited to examine the acceptability and interpretability of the SPUR model.

3. Validation Study – A two-arm cross-sectional study was designed and delivered that sought to provide early evidence of validity for the SPUR model in people living with T2D in both community and hospital settings using comparative PROMs and objective measures of MA.

The results of Phase 1 were used to inform the methodology of Phase 2. Therefore, this Chapter will present the Methods and Results sections for Phase 1 sequentially, followed by the Methods and Results Section for Phase 2.

3.2.2 Phase 1

3.2.2.1 Literature Review

3.2.2.1a Bespoke Framework Development

Given the multidimensional nature of the SPUR model (Social, Psychological, Usage and Rational) and limitations identified with methodologies for developing and reporting PROMs, multiple reference sources including the COSMIN[186] criteria and FDA PRO[187] validation guidance, in addition to several T2D PROM validation protocols and studies, were assessed to support the development of a bespoke validation framework for this study.[266–270] While the references provided a strong background for validation of psychometric properties, study sample, and setting, it also identified the need for a multi-comparator approach to support the validation of the SPUR model, originally derived from a wide range of PROMs mapped across the four major domains of S (Social), P (Psychological), U (Usage), and R (Rationale). A scoping literature review was conducted in January 2019 to determine the most suitable comparator PROMs to include in the validation study to assess convergent and construct validity. Furthermore, the literature review aimed to identify objective MA

measures that could be implemented within the final validation study to demonstrate concurrent validity of SPUR.

3.2.2.1b Search Strategy

The following databases were included in the search to ensure relevant studies were identified prior to extraction: PubMed, EMBASE, CINAHL, and WOS. A database search strategy was developed (Table 3.1), which included the use of MeSH terms that are used to catalogue and index specific vocabulary or terminology. The search strategy aimed to identify validated PROMs of MA in T2D. Key terminology and associated synonyms or related terms that were relevant to the condition of interest (T2D), outcomes (MA), and methods (PROMs) were extracted from either the title or abstract (referred to as [Title/Abstract]) as applicable to the search engine. Individual references within the included studies at the screening stage were reviewed for incidental inclusion of other eligible studies prior to further extraction. Any eligible study published between database inception and January 2019 were considered for screening.

Table 3.1 – Database Search Strategy

Disease/Condition Terminology	Diabetes Mellitus"[Mesh] OR "diabetes mellitus"[Title/Abstract] OR "t2dm"[Title/Abstract] OR "NIDDM"[Title/Abstract] OR "type 2 diabetes" [Title/Abstract]
Included Search Terminology	persisten* OR ("Patient Compliance") Or ("Patient compliance" OR "User compliance" OR "patient adherence" OR "treatment adherence" OR "Patient adherence" OR "Patient cooperation" OR "Patient non adherence" OR "Patient non compliance" OR "Patient nonadherence" OR "Patient non-adherence" OR "Patient noncompliance" OR "Patient non-compliance" OR "adherence to therapy" OR "adherence to treatment" OR "compliance to therapy" OR "compliance to treatment" OR "therapy adherence" OR "therapy compliance" OR "treatment adherence" OR "treatment compliance" OR "dosage adherence" OR "dosage compliance" OR "dose adherence" OR "dose compliance" OR "dosing adherence" OR "dosing compliance" OR "drug adherence" OR "drug compliance" OR "drug intake compliance" OR "drug regimen adherence" OR "drug regimen compliance" OR "medication adherence" OR "medication intake adherence" OR "adherence to pharmacotherap*" OR "compliance with pharmacotherap*") (patient reported*) or patient-report* or self-report* (Questionnaires OR interview) or (instrument* OR scale* OR Questionnaire* OR measure* OR methods OR outcome measurement* OR (test OR tests)) or tool* or survey* or PROM*
Publication Type	Clinical Studies, Validation Studies, Cross-sectional Studies, Longitudinal Studies, RCT
Publication Date	No origin date set (Database Inception) – Jan 2019
Population	Human - Adult

Abbreviations: RCT, randomised control trial

3.2.2.1c Inclusion & Exclusion Criteria

Studies were included if they were reported in English, study participants were over the age of 18 years, and a T2D diagnosis was confirmed for the study cohort in question. No definitive care setting was set as part of the inclusion criteria to widen the scope of the review.

Exclusion criteria were as follows: T1D or mixed study cohort where data between Type 1 and Type 2 participants were not discrete, cohorts of patients with mixed morbidity data whereby patient populations with T2D were unclear, SRs, patients with significant comorbidities that may affect MA results e.g., HIV, cancer, severe mental illness. Additionally, studies which used solely an objective MA measure e.g., MPR, without an additional PROM were excluded from the review.

3.2.2.1d Screening

Screening of abstracts and titles was initially conducted by the author to identify appropriate studies based on the inclusion and exclusion criteria. These criteria were also applied to the full-text screening phase of the literature review.

3.2.2.1e Mapping PROM Comparators

Following identification of validated PROMs through the literature review, a two-step approach was used to map potentially relevant PROMs as comparators to SPUR. Given the unique and holistic nature of SPUR, it was expected that several PROMs may be required as comparators. The first step involved identifying and reviewing which driver(s) of MA, or construct, each tool measured that could be mapped to one or more of the SPUR domains. The second step included item-to-item mapping between SPUR and the chosen model to identify correlations. This was a rudimentary analysis to explore items with similar wording/phrases that would look to capture similar data between PROMs and therefore, provide some indication of conceptual equivalence between models. It was hypothesised that using PROMs with high construct and item correlations to the SPUR model would provide the most meaningful results when compared as part of further validity analyses. This initial phased approach aimed to establish rudimentary construct validity and conceptual equivalence between SPUR and the comparative models. Descriptive statistics were used to determine the most common PROM across the included studies. The author mapped item-to-item correlations between the selected models, and the first supervisor performed the same mapping to prevent bias. Any discrepancies between either researcher during the mapping process were presented to the second supervisor for review before a final decision was made on the item correlation. These data were used inform the selection of appropriate PROMs as

comparators. License approvals, where relevant, were sought for PROMs included in the final validation study.

3.2.2.1f Objective Comparators

In line with guidance for PROM validation, it is recommended to incorporate objective measures as comparators of the primary outcome (concurrent validity), in addition to other PROMs. As a part of the scoping review, objective measures of adherence were identified, screened, and assessed for suitability e.g., previous use in people living with T2D. Descriptive statistics were employed to outline the frequency of using these measures in the reviewed studies and evaluate their perceived ease of implementation in the next phase of the validity study.

3.3 Results

3.3.1 Phase 1

3.3.1.1 Literature Review

The initial search identified 341 studies that were suitable for title/abstract screening (Figure 3.1). Initial exclusion removed 72 records prior to full text-screening. Full-text screening identified a total of 119 eligible studies after exclusion (n=150). Even though there were 119 included studies, some records reported >1 PROM, resulting in a larger total PROM sample (n=132). The MMAS was the most used model (n=75/132, 56.8%), followed by SDSCA (n=22, 16.7%) and MARS (n=10, 7.6%). From the 119 eligible studies, the review identified 12 unique PROMs. Table 3.2 provides a summary of the identified PROMs. In total, 15 studies were initially identified with an objective measure of MA that were assessed as suitable comparators for the concurrent validity of SPUR.

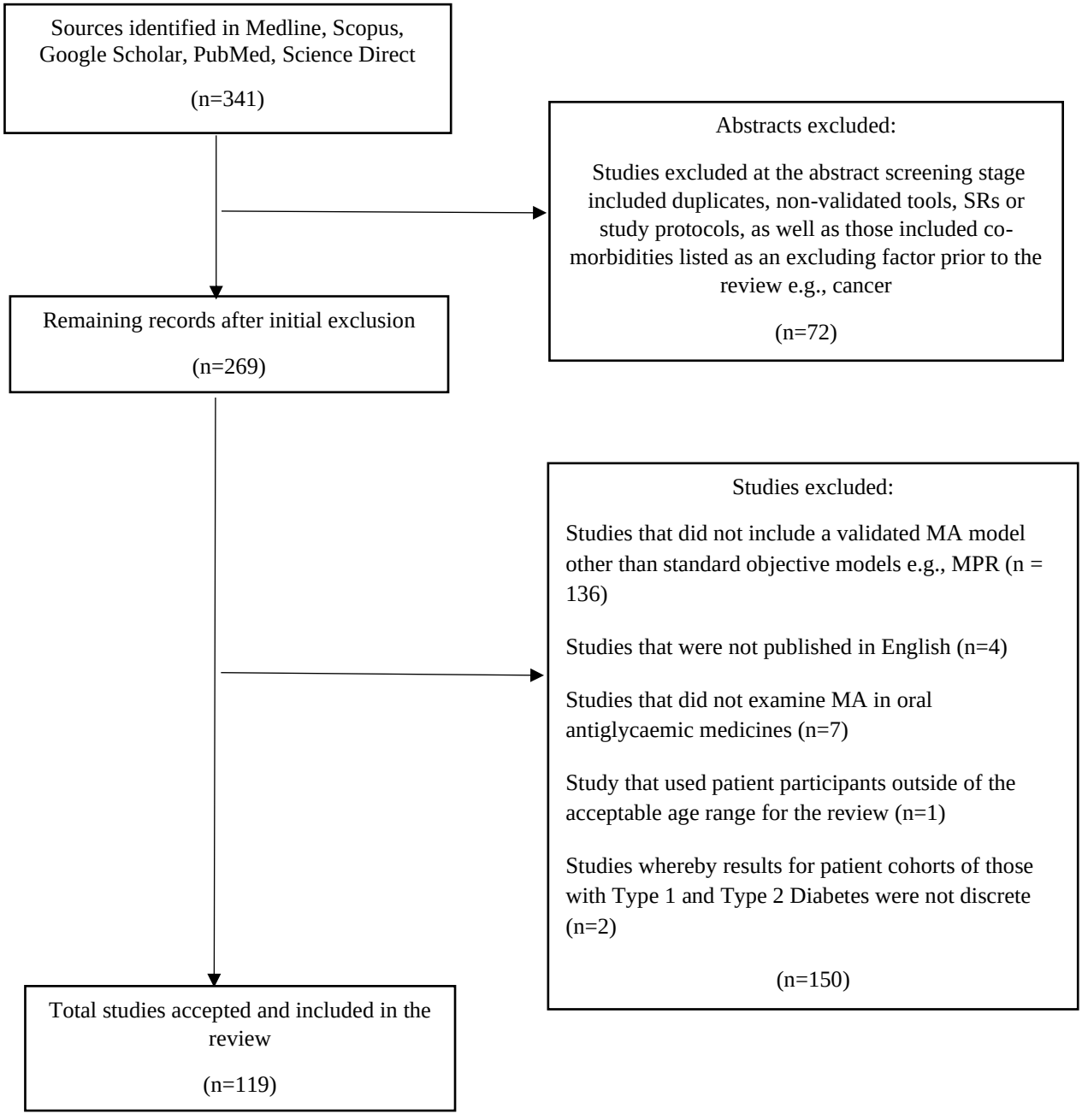


Figure 3.1 – Literature Review Inclusion/Exclusion Summary

Table 3.2 – A Summary of PROMs Identified in the Scoping Review

Identified PROMs	Frequency (n, %)
Adherence Barriers Questionnaire (ABQ)	1, 0.7
Adherence to Refills & Medication Scale (ARMS)[a]	8, 6.0
Beliefs about Medicines Questionnaire (BeMQ)[a]	6, 3.7
Diagnostic Adherence to Medication Scale (DAMS)	2, 0.7
Diabetes Care Profile (DCP)	1, 0.7
Drug-Attitude Inventory (DAI)	1, 0.7
Haynes-Sackett Questionnaire	2, 1.5
Medication Adherence Rating Scale 5-Item (MARS-5)[a]	10, 7.5
Morisky Medication Adherence Scale 8-Item (MMAS-8)[a]	75, 56.0
Medication Treatment Adherence Scale (MTA)	1, 0.7
Patient Activation Measure (PAM)[a]	3, 2.2
Summary of Diabetes Self Care Activities (SDSCA)[a]	22, 16.4
Total	132

Notes:[a]PROMs identified with ≥3 records that were selected for further review

3.3.1.1a PROM Mapping & Selection

Of the 12 PROMs, only those with ≥3 reported studies (n=6) were selected for further rudimentary construct analysis against the individual SPUR domains (Table 3.3). This decision was made to avoid incidental inclusion of novel PROMs with limited evidence to justify inclusion e.g., those with ≤2 reports would provide minimal scope for comparison of validity. Within each selected PROM, items or sets of items were reviewed to provide an indication of relative construct comparability to each SPUR domain e.g., the BeMQ contains items related to medicines necessity and concerns, which therefore mapped comparatively as a construct against the Rational domain for SPUR. Once the initial round of mapping was complete, it was identified that a PROM with construct equivalence for the Social domain was lacking. A brief literature search identified the DTSQ as a potentially suitable model. The DTSQ was identified with a very weak link to the Social construct, with only one item pertaining to a patient's engagement with a friend. Notably however, the other comparative PROMs contained no items related to the Social domain. Hence, it was agreed that although

this one item may not be completely sufficient to fully explore the validity of the Social domain, the model should be retained to given the strong association between treatment satisfaction and MA.[190] Of the seven total PROMs, equivalence with the Rational domain was most common (n=5/7, 71.4%). None of the PROMs provided a multidimensional model that covered >2 SPUR domains.

Table 3.3 – SPUR Domains & Comparative PROMs

PROM	SPUR Domain			
	Social	**Psychological**	**Usage**	**Rational**
ARMS	No	No	Yes	No
BeMQ	No	Yes	No	Yes
DTSQ	Yes	No	No	Yes
MARS-5	No	No	Yes	Yes
MMAS-8	No	Yes	Yes	No
PAM	No	No	No	Yes
SDSCA	No	No	No	Yes

After construct/domain mapping, the selected PROMs were assessed for their equivalence through item-to-item mapping against SPUR (Table 3.4). This method provided quantitative data on correlations between the 45 Likert-scale items included in SPUR (Appendix A) and the comparator PROMs. The BeMQ, MMAS-8, and Patient Activation Measure (PAM) were most strongly correlated at an item level accounting for 35.6% (n=16/45), 22.4% (n=11) and 26.7% (n=12) of item correlations, respectively. While not necessarily a direct measure of MA, the DTSQ was included in the item-to-item mapping and produced a strong correlation (37.8%, n=17). A total of 37 SPUR items (82.2%) were mapped across all comparators.

Table 3.4 – Item-to-Item Mapping (SPUR *vs* Comparator PROMs)

SPUR Item	MMAS-8	PAM	DTSQ	BeMQ	SDSCA	ARMS	MARS-5	Item Mapped?
1				B9				y
2								
3			D7					y
4								
5								
6		P2						y
7								
8								
9			D8	B1				y
10								
11						A2		y
12		P8	D8					y
13								
14	M3							y
15	M3			B11-13				y
16	M8					A1	M1,2,3,4,5	y
17			D4					y
18						A12		y
19	M8	P3	D2,D8					y
20		P6						y
21						A12		y
22	M4		D4,D5					y
23		P4	D6	B10				y
24	M1	P7	D4					y
25	M1-2	P7	D4					y
26			D3	B6				y
27	M6			B16		A2,A6	M3	y
28				B7				y
29								
30		P10						y
31				B9				y
32		P8	D6					y
33		P8	D6					y
34				B15				y
35			D2	B15				y
36			D1	B2				y
37			D1	B15		A2		y
38		P1-2						y
39	M6	P2-5		B4-B5				y
40	M3			B3		A6,A7		y
41						A12		y
42			D1,D6					y
43	M7			B1				y
44				B14				y
45			D2					y
Mapped (n, %)	11, 22.4%	12, 26.7%	17, 37.8%	16, 35.6%	0.0	8, 17.8%	2, 4.4%	
Total SPUR Mapped (n, %)								37, 82.2%

The four PROMs with the highest item-to-item correlations also provided coverage of all four SPUR domains in the construct comparison. Hence, these PROMs were initially selected as appropriate models to include in the validation study. License approvals were sought for the selected PROMs, however only two were granted. These were for the use of DTSQ and BeMQ, respectively. The DTSQ has previously reported satisfactory factor loadings (0.67-0.90) for a confirmed two-factor structure in addition to adequate internal consistency reports for the scale tested with different English speaking populations (α=0.79-0.82).[271,272] Similar validity metrics in terms of factors loadings (~0.7-0.8) for the original 4-factor BeMQ structure are reported by Horne *et al*.[188] An acceptable average internal consistency estimate (α=0.75) was identified among a population of patients diagnosed with T2D. The ARMS and MARS-5 were then chosen as two potential options to provide construct equivalence for the Usage domain in lieu of the MMAS, however these were poorly correlated and license approvals for use were not provided by the original authors. To address this, a decision was made to investigate similar PROMs with less evidence of validity in T2D population with available licenses for use. The MARS[189] was a PROM originally developed for English speaking patients with mental health diagnoses such as schizophrenia. However, this model was derived using items from both the MMAS-8 and DAI, both of which have been validated in T2D populations and therefore provided moderate construct equivalence when mapping against the SPUR domains for both Usage and Rational.[273] Furthermore, there has been uptake of the model in mixed populations with mental health diagnoses and T2D (α=0.75).[273–275] Notably, the item-to-item mapping method to explore correlations was a relatively rudimentary approach given that items may have had similar wording, hence a single item may have been mapped more than once when compared with SPUR, providing potentially exaggerated correlations. To provide further evidence of suitable conceptual or construct equivalence at an item level, the individual PROMs were reverse correlated to

determine the proportion of items within each model that had mapped to SPUR (Table 3.5). Each PROM demonstrated significant reverse item-to-item mapping with individual SPUR items (n=30/45, 66.7%), with BeMQ, DTSQ and MARS (See the comparator PROMs in Appendix B) reporting 77.8%, 100.0% and 80.0% item-mapping, respectively. As a replacement for MARS-5 and MMAS, the MARS model provided coverage for the Usage domain. In addition, the BeMQ contains two subscales, BeMQ-Specific and BeMQ General, which map to the Rational and Psychological domains, respectively. Hence, comparators for all four major SPUR domains were incorporated. All three licenses were granted for use of the PROMs in the validation study.

Table 3.5 – Reversed Item-to-Item Mapping (Comparator PROMs *vs* SPUR)

PROM	**BeMQ**	**DTSQ**	**MARS**
Items	1[a]	1	1
	2	2	2
	3	3	3
	4	4	4
	5	5	5
	6	6	6
	7	7	7
	8[a]	8	8
	9		9
	10		10
	11		
	12		
	13		
	14		
	15		
	16		
	17		
	18		
Total (n, %)	14, 77.8%	8, 100.0%	8, 80.0%

Notes:[a]Grey-scale cells indicate that the SPUR item did not have a comparator item for the individual PROM

3.3.1.1b Objective Comparator Selection

Only 15 of the 119 studies included in the review used an objective measure of adherene, 53.3% (n=8/15) of them implemented MPR. Given the small sample size of included studies that incorporated an objective measure, excluded studies (n=150) were also reviewed. In total, 98 of the excluded studies reported an objective MA measure. MPR remained the most common MA measure in 41.8% (n= 41/98) of eligible reports compared to other methods such as the PDC (26.5%, n=26/98), which was the second most common objective measure. MPR and PDC have been shown to provide similar estimates of MA in populations with varying clinical conditions, including T2D.[276] The previous evidence of validity in addition to the high prevalence of reporting of MPR in the scoping review supported the decision to include this model as an objective comparator of MA in the validation study.

HbA_{1c} was the most common clinical measure of MA, reported in 36.9% (n=44/119) of the included studies. Although HbA_{1c} is not a specific measure of MA, it provides a reliable clinical measure of overall T2D self-care, which includes significant correlations ($p<0.05$) between glycaemic control and MA.[277] HbA_{1c} was therefore chosen as an additional objective comparator to provide evidence of concurrent validity against the SPUR model.

3.4 Methods

3.4.1 Phase 2

3.4.1.1 Pilot Study

3.4.1.1a Study Population & Sample Size

The pilot study was designed and delivered to examine face/content validity, acceptability, and interpretability of SPUR across three major stakeholder groups. The stakeholders included:

1. People living with T2D that regularly take medicines for their condition.
2. Community pharmacists (CP) that have regular contact with the target patient group.
3. Medicines optimisation (MO) field experts with experience of adherence reviews e.g., MO pharmacists

In line with recommended best practice for Patient and Public Involvement (PPI) as well as international PROM development methodologies, service-users (patients) should be directly involved in the review and design of outcome measure.[186,187] Therefore, one of the aims of the pilot study was to demonstrate face/content validity and acceptability of the SPUR model with people living with T2D. The pilot employed a convenience and snowball sampling method, with a recruitment target range of 10-30 patients (~5-10% of final study population estimated, See Section 3.4.1.2c).

Furthermore, it is recommended that HCPs with both relevant and diverse experience should be involved in outcome measure development.[186,187] Therefore, to supplement feedback on the acceptability of the tool in addition to patients, CPs were included to represent a cohort of HCPs that directly engage patients in tackling issues regarding MA. This stakeholder group was chosen to help determine the perceived acceptability of the tool, as well as providing information on the perceived feasibility of using SPUR in practice post-validation as a means of evaluating interpretability of the model. The estimated sample size was approximately 5-10 participants who were recruited using convenience and snowball sampling methods.

Experts in MA or MO were chosen based on the rationale for determining the perceived usefulness of the SPUR tool to profile behaviour, and as a result determine MA. MO HCPs use several methods to evaluate MA with patients in practice, and therefore feedback from this cohort is particularly valuable in determining the role of the SPUR model as such a

method and the perceived utility/interpretability of the PROM. The estimated sample size was approximately 5-10 participants, again recruited using convenience and snowball sampling methods.

The additional recruitment inclusion criteria for the patient cohort of the pilot study as well as HCP recruitment are described below.

3.4.1.1b Patient Recruitment

Local pharmacies in Richmond and Kingston as well as local support groups, such as Diabetes UK, were contacted to request participation in the pilot. Informed consent was requested from eligible patients using a bespoke consent form (Appendix C) prior to participation or data collection. Patients were also provided with a participant information sheet (PIS) (Appendix D).

Inclusion Criteria

1. Patients aged 18 years and over.
2. Patients diagnosed with T2D.
3. Patients using at least one oral anti-diabetic medicine (patients taking insulin in addition to oral anti-diabetic medication are included) and a minimum 6-month history of prescriptions for T2D.
4. Capable of understanding and willing to provide voluntary informed consent before taking part in the study.

Exclusion Criteria

1. Patients diagnosed with T1D
2. Patients diagnosed with T2D with less than 6 months of pharmacological treatment
3. Patients with a T2D diagnosis who are controlled using diet alone
4. Patients who are illiterate or unable to complete the questionnaire due to a language barrier
5. Mentally incapacitated patients e.g., severe learning disability/severe dementia

6. Patients with extremely severe psychiatric co-morbidities
7. Patients involved in a Clinical Trial of an Investigational Medicinal Product (CTIMP) at the time of the study

3.4.1.1c Community Pharmacist/Expert Recruitment

Similarly, local community pharmacies in Kingston and Richmond were targeted for the recruitment of CPs. A CP specific information sheet (Appendix E) and consent form (Appendix F) were designed and provided prior to participation. Expert participants were recruited from University Hospital Lewisham (UHL) through a local pharmacy-led MO service (Lewisham Integrated Medicines Optimisation Service (LIMOS)) facilitated by a joint project taking place between Kingston University (KU) and UHL at the time. HCPs were provided with a separate information sheet and consent form prior to data collection (Appendix G & H). No specific sample characteristics were defined as part of the recruitment strategy (e.g., years of experience, previous roles, level of additional post-graduate education) to ensure a broad sample could be included in this arm of the study.

3.4.1.1d Data Collection

The pilot study used a mixed-method approach with the inclusion of SPUR model in addition to a quantitative Likert scale survey, which included participant demographics and qualitative feedback on the SPUR model (Appendix I – Patient Questionnaire, Appendix J – HCP Questionnaire). The main SPUR questionnaire for patients contains 45 Likert scale (1-5) questions with 1 being strongly disagree, to 5 being strongly agree. These 45 items cover the 4 key adherence domains outlined as part of the SPUR methodology: Social, Psychological, Usage and Rationale. The additional data collection items for both the Patient Questionnaire and the HCP Questionnaire are outlined below.

Patient Questionnaire

Four demographic questions were included as well as nine feedback questions, which were both quantitative (n=5) and qualitative (n=3) in nature, with the latter enquiring about recent HbA_{1c} results. The demographic questions included in both the HCP and patient questionnaire cover the following characteristics: age, ethnicity, gender, and highest level of education. Certain aspects of the SPUR model design were examined such as the acceptability of the questionnaire length, patient confidence in completing the questionnaire independently (which would be required in the full validation study) and the perceived relatability of the questions to their T2D diagnosis. Patients were also given the opportunity to highlight specific questions or areas of the questionnaire they felt were inappropriate or unable to answer. Hence, the aim of the patient data collection tool was to provide preliminary face/content validity of the SPUR questionnaire.

HCP Questionnaire

The questionnaire was designed specifically for HCPs and included the same 45-item SPUR model for review, as well as four demographic and six feedback questions, one of which was qualitative. The demographic items included in the HCP questionnaire match those outlined in the patient questionnaire. The feedback items for the HCP questionnaire examined the perceived usefulness of the SPUR tool as well as the acceptability of it as a potential measure of MA. HCPs were given the opportunity to highlight questions or areas of the questionnaire they felt were inappropriate or which they feel patients would be unable to provide a clear answer for. Both the HCP and the patient cohort were given the opportunity to comment on the length of the SPUR tool.

3.4.1.1e Data Analysis

Data were collated and analysed in Microsoft Excel software. Descriptive statistics, such as the mean, were calculated for quantitative Likert scale responses for both the patient and

HCP cohorts. The results of the mean scores for individual items were evaluated to determine potential trends in participant responses based on socio-demographic information.

3.4.1.1f Ethical Approval

Ethical approval for the pilot study was provided by the KU Research Ethics Committee (REC) on 25th March 2019. The ethical application title and allocated study number for this pilot project is: 1819 066.1 – 'Validating an adherence measuring tool and evaluating its feasibility as a profiling tool for personalised medicines optimisation interventions by pharmacists'.

3.4.1.2 Validation Study

3.4.1.2a Study Setting

This study, titled 'Validating a Medication Adherence Tool in Type 2 Diabetes (VMATT2)', was conducted as a multi-arm, non-interventional, cross-sectional study among people living with T2D in England between August 2019 and May 2021, with a view to provide early evidence for the validity of SPUR as a PROM of MA.[278] The study objectives are described in Section 3.1.4. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) cross-sectional checklist.[279]

The preliminary arm was conducted in community pharmacies based in Southwest London. The second study arm was based at a secondary care site (Kingston Hospital NHS Foundation Trust) in Southwest London.

3.4.1.2b Study Population

The same patient eligibility standards for patients living with T2D were applied to both the community pharmacy and hospital recruitment. The inclusion and exclusion criteria were as follows:

Inclusion criteria

1. Patients aged 18 years and over.
2. Patients with diagnosed T2D.
3. Patients using at least one oral anti-diabetic medicine (patients taking insulin in addition to oral anti-diabetic medication are included) and a minimum 6-month history of prescriptions for T2D.
4. Capable of understanding and willing to provide voluntary informed consent before taking part in the study.

Exclusion Criteria

1. Patients with diagnosed T1D
2. Patients diagnosed with T2D with less than 6 months of pharmacological treatment.
3. Patients with a T2D diagnosis who are controlled using diet alone
4. Patients who are illiterate or unable to complete the questionnaire due to a language barrier
5. Mentally incapacitated patients e.g., severe learning disability/severe dementia
6. Patients with extremely severe psychiatric co-morbidities
7. Patients involved in a CTIMP at the time of the study

3.4.1.2c Sample Size

Raosoft[280] software was used to determine the minimum representative sample size of the population for the study. The initial sample was based on public health data to inform the number of patients diagnosed with diabetes in the immediate population for Richmond, Kingston, and Sutton (n=25,213 patients) in 2019.[281] A 1:9 ratio of type 1 to T2D (n=22,692) was applied before a final estimation using Raosoft, which resulted in a final minimum

sample of 378 patients with a 5% Margin of Error (MoE) and a 95% CI. A recruitment target between community and hospital settings was set at a ratio of roughly 1:1.

3.4.1.2d Recruitment & Sampling Technique

Community Arm Recruitment

Community pharmacies located in Richmond and Kingston were contacted to recruit CPs for the study. CPs were asked to sign a consent form (Appendix K) to participate as a study pharmacy prior to the provision of all relevant study materials, this included a CP information sheet (Appendix L). CPs were provided with the eligibility criteria to recruit suitable patients living with T2D from the community pharmacy setting. The pharmacists actively recruited patients and provided them with the consent form (Appendix M) and PIS (Appendix N) prior to participation and collection of any data relevant using the study questionnaire. Patients were also asked to provide consent for access to their pharmacy record by the designated CP to provide objective MA data for the study. Given the nature of access to community pharmacy settings, a convenience sampling method was applied, whereby patients accessing the pharmacy were actively screened for study eligibility prior to participation. CPs were provided with a £10 voucher of choice from a local retailer for each patient recruited into the study. Funding for this incentivisation was provided through the Health Education Foundation grant that was awarded to the thesis author as part of his PhD.

Hospital Arm Recruitment

Prior to any invitation to participate in the study or engagement from the author, the patients' direct clinical care team were first contacted to identify and approach potentially eligible patients to discuss the option of a discussion with the author. This approach was taken as some patients may have been acutely unwell and/or unwilling to participate while in the

hospital setting. Potentially eligible patients were those that met the inclusion/exclusion criteria and were identified with a T2D diagnosis upon admission or were registered with a suitable outpatient clinic and were thus flagged as potential participants. The clinical care team notified the author of eligible patients who expressed an interest in participating.

Following an expression of interest, the author approached patients to complete the consent process (Appendix O) and provide further information, including the PIS (Appendix P). The consent form also included a statement providing consent for the researcher to access the patient's individual clinical care record and Summary Care Record (SCR), where available, to collect additional clinical data relevant to the study e.g., comorbidities and pharmacy medication records. Patients were then asked to complete the study questionnaire, prior to a copy of the signed consent form and a written declaration of study participation being added to individual patient notes.

A homogenous purposive sampling strategy was employed for this arm of the study. This method identifies and pursues a research sample from a population where all participants share similar pre-defined characteristics relevant to the study objectives. This sampling technique is concordant with PRO validation protocols, which encourage selection of the target group for recruitment *vs* random convenience sampling.[186,187,266–270] This method reduces inter-rater variability and ensures that the sample is recruited in an efficient and timely manner in line with the rate of admission and outpatient clinics for engagement with eligible people living with T2D seen within the study duration.

3.4.1.2e Data Collection

Data Collection Tool

The full data collection questionnaire (Appendix Q) included the original 45-item SPUR model. As outlined in the Phase 1 Results (Section 3.3.1), three additional PROMs were selected as comparators and included in the data collection tool (BeMQ, DTSQ, MARS). Additional questions were included to gather information about the sociodemographic background of participants (age, gender, income, ethnicity) and relevant clinical details, such as their number of prescribed antiglycaemic agents, comorbidities, and BMI. The literature review also identified two objective comparators, HbA_{1c} and MPR, that were included in the data collection tool. This information was collected through patients' self-report or consented medical record review (in the secondary-care arm only).

Data Collection Method

Post-recruitment, a paper copy of the questionnaire was provided to participants in either the community pharmacy or hospital setting. For each setting, participants were given as much time as possible to complete the questionnaire by themselves. Typically, participants from the community pharmacy setting completed the questionnaire before leaving the pharmacy, whereas those in the hospital setting would sometimes be left for a few hours to complete the questionnaire before the author returned to the ward or outpatient clinic to collect the materials. Upon completion, questionnaires were assessed to ensure all answers had been provided. If items were missed, participants were informed and provided with the opportunity to fill in the items as well as given information by the author on why missing items should be addressed in order to improve the results of the study. On some occasions, amendments to improve accessibility were made to support patients in self-completing the questionnaire. For example, some patients with partial loss of sight requested enlarged questionnaires, which were then printed and provided. In a very small number of cases (n=<5) in the hospital setting, patients with more severe loss of sight were able to participate in the study with the

author dictating the questionnaire. To avoid bias, a member of the clinical team on the ward or outpatient clinic was asked to verbally verify to the participant that the contents of the questionnaire were in line with the descriptions from the author. The clinical team members were also asked to verify the completion of consent forms for the participant, with verbal confirmation that these were complete and had been added to the participant's record in line with the study protocol.

3.4.1.2f Data Analysis

SPUR Scoring Methodology

As previously outlined, SPUR contained 45 Likert scale items with 1 being strongly disagree, to 5 being strongly agree. To avoid over-expression of a positive effect direction from participant responses, 17 items (37.8%) were constructed as negative statements.[282] The total Likert-scale responses for individual items were added (negative statements were reverse coded) for the SPUR tool and divided by the potential total score (5×45) and converted to a percentage score to determine an overall score for the model that reflected MA and related behaviour. This same method was used for each domain (S, P, U & R) by adding the total Likert-scale responses for individual items for each subscale, with higher scores reflecting a greater likelihood of adherence. This approach was taken to improve the interpretability of SPUR scores when compared with data on objective adherence, such as MPR, which is widely reported as a percentage in the literature.

Factor Analyses

Exploratory Factor Analysis (EFA) was conducted in line with guidance such as the COSMIN criteria[186] to identify subscales within a group of questionnaire items. To determine if the database was suitable for analysis, the Kaiser-Meyer-Olkin (KMO) measure of

sampling adequacy and Bartlett's test of sphericity were both calculated.[283] Eigenvalues >1, visual inspection of a matching inflection points on a scree plot, in addition to Monte Carlo parallel analysis (MCPA) were used to identify initial factors.[284] MCPA is a statistical method that is used to determine the number of factors in a dataset by comparing eigenvalues obtained from the study data to those obtained from randomly generated datasets of the same size that may improve the accuracy and reliability of factor analysis.[285] The structure of the SPUR tool in the specific study population was explored using Principle Axis Factoring (PAF) with Direct Oblimin rotation. Direct Oblimin was chosen as an example of an oblique rotation. Oblique rotations, compared to orthogonal rotations, are recommended when there is evidence or an assumption that factors within a model will be partially correlated, as was the case for SPUR and its various determinants of MA behaviour.[286] Factor loadings greater than 0.32 were considered valid.[287] Furthermore, inter-factor correlations were observed using Spearman's rank correlation coefficient (ρ) with a significance level of $p<0.05$.

Reliability Analyses

Internal consistency estimates of reliability for the entire SPUR tool, as well as for individual subscales, were calculated using Cronbach's alpha (α). A value of alpha greater than or equal to 0.8 was considered to be strong evidence of reliability, although figures of >0.7 are defined as appropriate through methodologies such as the COSMIN crtieria.[186,288]

In additional to internal consistency, test-retest reliability measures were developed whereby a sub-sample of participants from both the community and hospital arm were to be recruited to recomplete the questionnaire to assess correlations (Spearman's Rho) between completed pairs of measures at two separate time intervals. The interval outlined in the protocol was set as 6-months for the study, but due to Covid-19 this was not completed. The author conducted

factor and reliability testing to determine the overall suitability of the original SPUR-45 tool or any revised models for further analysis of psychometric properties.

Construct, Convergent & Discriminant Validity

As described in Section 3.3.1, several PROMs were identified as a result of the literature review and were selected to support the development of evidence for construct, convergent, and discriminant validity of the SPUR model: MARS,[189] BeMQ-Specific, BeMQ-General,[289] and the DTSQ.[290]

Relevant scoring protocols were used to determine the results of each PROM. It was expected that higher scores for each PROM (e.g., high self-efficacy, treatment satisfaction, perceived necessity and/or avoidance of harm) would be positively correlated with higher scores for the SPUR tool and the comparative subscale/domain as a strong predictor of MA. Individual SPUR factors were expected to produce stronger correlations with their comparative PROM e.g., MARS score predicted to correlate most strongly with the Usage factor score. These individual assessments of convergent validity between PROMs, individual factors, and overall scores were used to provide evidence of construct validity for the SPUR model.[186]

Concurrent Validity

In addition to subjective PROMs, the previously conducted literature review was used to support the selection of objective comparators or pseudo gold-standard measures of MA to provide evidence of concurrent validity. The objective comparators implemented in this study were HbA_{1c} and the MPR. The most recent HbA_{1c} result (% and mmol/mol) within the past six months was obtained through either self-reported (community arm) methods or derived from the patient medical record (PMR) with consent. HbA_{1c} cut-offs of ≤6.5% (48 mmol/mol) for single agent or ≤7.0% (53 mmol/mol) for multi-agent or single

hypoglycaemic agent medication regimens, as reported during socio-clinical data collection, were used to determine MA. MPR, a simple measure of MA, was used to determine a representative MA as a percentage over a 6-month period using the following formula:

$$MPR = \frac{Number\ of\ doses\ prescribed\ to\ the\ patient}{Number\ of\ days\ within\ review\ period\ (Approx\ 180\ days)} x\ 100\%$$

The PMR or SCR provided the MPR data for community and hospital participants, respectively. Adherence was determined by a cut-off of MPR ≥80%.[291] Significant correlations (p<0.05) between PROMs, objective data, and SPUR were tested using Spearman's rank correlation coefficient (ρ). Wilcoxon signed-rank tests were used to investigate mean adherence score differences between PROMs and objective measures.

Known Group Validity

Correlation analyses were conducted as a means to provide evidence for known group validity. Specifically, the study sought to evaluate the strength and significance of relationships between SPUR and socio-clinical factors that are known to have significant interactions with MA and related determinant behaviour. Based on the literature, the study hypothesised that there would be a significant increase in MA with age and income, and a decrease in patients who were prescribed a greater number of antiglycaemic agents, reported a higher number of comorbidities, or who had higher BMI values.[292–295] Between-group analyses using Kruskal H Wallis tests (>2 groups) or Wilcoxon signed-rank tests (paired groups) were implemented to investigate significant differences for variables such as gender, ethnicity, and recruitment setting (hospital *vs* community) on subjective and objective measures of MA. Effect sizes were determined using Cohen's d or Glass's Δ, with the latter being reported in cases where there were significant differences in SD between groups.

The initial data were collated in Microsoft Excel prior to exportation and data analysis using IBM SPSS Software Version 26.0. Consistently, non-parametric analyses were applied during the study e.g., Spearman's rank correlation coefficients, however for each data set, the Shapiro-Wilk test was conducted to determine the distribution of data. Non-parametric testing (e.g., Spearman's) was applied in instances whereby non-normal data distribution was identified using this method (Shapiro-Wilk, $p<0.05$). The mean (x) and SD were used to express continuous data or ordinal data, while sample number (n) and percentage (%) were used to report categorical data.

3.4.1.2g Ethical Approval

The KU REC provided approval the community arm of the VMATT2 study in August 2019 (1819.081.1). To facilitate the NHS ethical approval, PPI was sought from a local patient diabetes support group at Kingston Hospital in June 2019 to review the face and content validity of research materials that were being developed for use within the hospital. In addition to the suitability and interpretability of items, the participants' experiences with poor adherence were discussed, which supported the study's relevance. Although no changes were made to the questionnaire and participants were not involved in the study, an update for the patients/public on the outcome of the study was agreed post-completion, which was facilitated through public engagement forums within the Trust. Approval for the secondary-care arm of VMATT2 was provided by the NHS Health Research Authority (ID: 270768) by REC review (Ref: 19/NW/0685) in December 2019. All study participants provided written informed consent before taking part in either arm of the study.

3.5 Results

3.5.1 Phase 2

3.5.1.1 Pilot Study

3.5.1.1a Patient Pilot Results

In total, 52 patients were invited to take part in the pilot study with 15 being successfully recruited providing a response rate of 28.8%. The socio-demographic characteristics of participants were collected and are described in Table 3.6. Participants were generally older, female, white, as well as predominantly educated to degree level.

Table 3.6 – Patient Pilot Study Sample Characteristics

Parameter (n=15)	**Number (n,%)**	**Mode**
Age		60-69
30-39	2, 13.3%	
40-49	3, 20.0%	
50-59	2, 13.3%	
60-69	5, 33.3%	
70-79	2, 13.3%	
80+	1, 6.7%	
Gender		Female
Male	5, 33.3%	
Female	10, 66.6%	
Ethnicity		White
White	7, 46.7%	
Mixed/Multiple Ethnic Groups	0	
Asian/Asian British	3, 20.0%	
Black/African /Caribbean/ Black British	5, 33.3%	
Other	0	
Education		Bachelors Degree or Equivalent
No formal education	1, 6.7%	
GCSE or Equivalent	1, 6.7%	
A-Level or Equivalent	3, 20.0%	
Bachelors Degree or Equivalent	6, 40.0%	
Post-graduate Degree or Equivalent	4, 26.7%	

Abbreviations: GCSE, General Certificate of Secondary Education

Results from the Likert-scale items (n=5) included in the patient pilot survey indicated the overall participants agreed that SPUR questions were easy to answer (Table 3.7). Notably, the lowest score was in response to the statement ‘I am happy with the length of the questionnaire’ with a mean of 2.8, indicating that most participants would either disagree or were unsure about the length of the SPUR model. None of the individual SPUR items were

highlighted by patients in terms of being misunderstood or poorly worded. Additionally, despite an ambivalent response to the length of the questionnaire as well as completing SPUR independently, all participants returned the SPUR surveys with 100.0% item completion rate. Encouragingly, 46.7% of participants were able to provide their most recent $HbA1_c$ result within the last 6 months. This finding demonstrated some awareness of $HbA1_c$ monitoring among patients recruited in the community-pharmacy setting, which was an important consideration given the potential impact of recall bias within this arm of recruitment whereby easy access to medical records and data such as HbA_{1c}, may be limited.[296]

Table 3.7 – Patient Pilot SPUR Feedback Results

Statement	Mean Score (n=15)
The questions were easy to answer	4.3
I am happy with the length of the questionnaire	2.8
I would be happy to complete the questionnaire by myself	3.7
I believe this questionnaire could help improve my relationships with medicines	3.5
The questions are relevant to my condition	4.1

3.5.1.1b HCP Pilot Results

Six of 10 HCPs invited to take part in the pilot were successfully recruited, providing a response rate of 60.0%. The socio-demographic characteristics of the HCPs were collected and reported in Table 3.8. There was an even distribution between CPs (n=3) and experts in MO (n=3), with the latter group consisting of three MO pharmacists within the UHL LIMOS team.

Table 3.8 - HCP Pilot Study Sample Characteristics

Parameter (n=6)	Number (n,%)	Mode
Age		40-49
20-29	2, 33.3%	
30-39	1, 16.7%	
40-49	3, 50.0%	
50-79	0	
80+	0	
Gender		Female
Male	1, 16.7%	
Female	5, 83.3%	
Ethnicity		White
White	3, 50.0%	
Mixed/Multiple Ethnic Groups	0	
Asian/Asian British	2, 33.3%	
Black/African /Caribbean/ Black British	1, 16.7%	
Other	0	
Education		Post-Graduate Degree or Equivalent
No formal education	0	
GCSE or Equivalent	0	
A-Level or Equivalent	0	
Bachelors Degree or Equivalent	2	
Post-graduate Degree or Equivalent	4	

Similarly to patient group, the HCP response to the length of SPUR was neither definitively positive nor negative (Table 3.9). Overall, SPUR had high perceived acceptability and usability across the HCP cohort, with most participants strongly agreeing that the questions were patient appropriate, would be of value with respect to patient-medicine relationships, and that they would be happy integrate SPUR as part of MA assessment in their own practice. No statistically significant quantitative differences can be drawn from the results with this sample size, however the average mean difference in scores across all items between CPs and MO experts was small (Mean difference = 0.37), which may be somewhat indicative of agreement between these groups in the pilot.

Table 3.9 - HCP Pilot SPUR Feedback Results

Statement	Mean Score (n=6)
I feel the questions are patient appropriate	4.6
I feel the length of the questionnaire is appropriate	3.2
I would be happy to use this questionnaire to assess adherence for my patients	4.8
I believe this questionnaire can help improve patient relationships with their medicines	4.6
The believe the questionnaire would be easy for patients to complete by themselves	4.2

3.5.1.1c Pilot Conclusions

The results of this pilot provided early evidence of face and content validity for the SPUR model. The length of SPUR was noted as the area with the least positive agreement from participants in both cohorts and was considered to be the largest barrier to acceptability, interpretability, and potential clinical utility of the model. However, the 100.0% completion rate of the patient surveys despite the survey length, in addition to high mean scores for other indicators of acceptability and interpretability (e.g., ease of use, relevance of items) across both cohorts meant that no changes were made to SPUR following the pilot. Furthermore, it was considered appropriate to include all items within further validity analyses to determine which items may be statistically redundant across a larger study sample size. One limitation of note was the exclusion of general practice pharmacists or other HCPs, including nurse practitioners that take an active role in patient medicines management. Given that the primary care setting is well suited for medication review, particularly in the context of medication initiation and discontinuation, HCPs involved in these activities may have provided additional insights to support the review of the SPUR model. Future work will look to evaluate the SPUR model with a wider range of HCP cohorts.

3.5.1.2 VMATT2 Study

3.5.1.2a Study Sample Characteristics

The study met the minimum sample size and included 378 participants, with 178 (24.7% response rate based on those invited plus additional exclusion, n=198/799) and 200 (82.0% response rate based on those invited plus additional exclusion, n=218/266) from the community and secondary-care arms, respectively (Figure 3.2). The main reasons for exclusion involved the disclosure of an excluding diagnosis (n=5), a lack of fluency in English to participate (n=9), and individuals who declined to complete the questionnaire after starting the process (n=7).

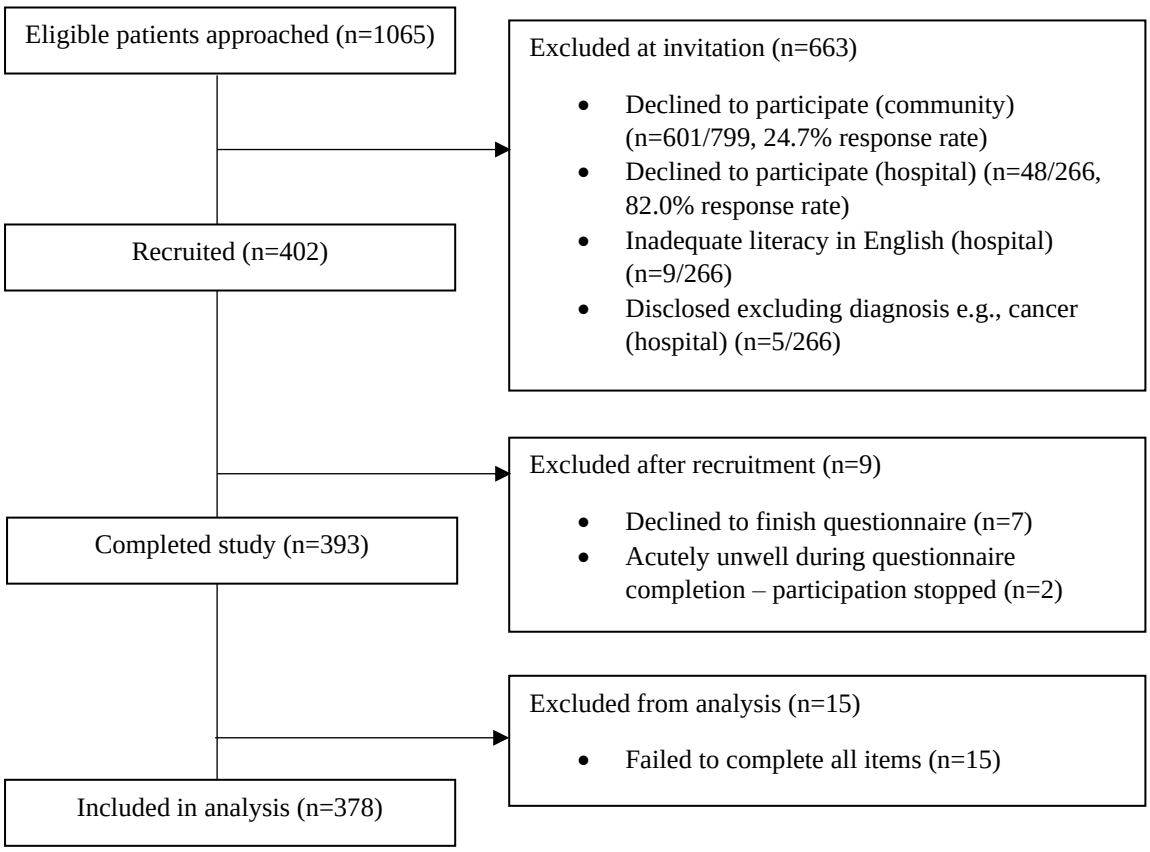


Figure 3.2 – Flowchart of Study Participant Sampling Procedure

For socio-demographic variables including age, education, and income, data were collected and reported in Table 3.10. The most common age group was 60-69 years old (25.4%, n=96/378). Education was predominantly reported at GCSE level or equivalent (32.3%, n=122) and more than half of the respondents indicated that they were retired at the time of participation in the study (51.9%, n=196).

Almost two-thirds of the sample were white (61.1%, n=231) and female participants made up 40.2% (n=152) of the total cohort. BMI data were available for 92.9% of the participants (n=351/378) with a mean BMI of 29.35 ± 6.17, indicating that a significant proportion of participants were above their recommended weight. Additionally, less than half of the sample (39.5%, n=105/266) met a $HbA1_c$ target of ≤7.0% (53 mmol/mol), with a mean for the sample population of 7.7% (60.29mmol/mol). The mean number of antiglycaemic agents and comorbidities were 1.92 ± 0.90 and 4.70 ± 3.14, respectively.

Table 3.10 – Study Sample Characteristics

Parameter (n=378)	Number (n,%)	Mode (mean±SD, range)
Age		60-69
18-29	3, 0.8%	
30-39	8, 2.1%	
40-49	42, 11.1%	
50-59	58, 15.3%	
60-69	96, 25.4%	
70-79	94, 24.9%	
80+	77, 20.4%	
Gender		Male
Male	222, 58.7%	
Female	152, 40.2%	
Other	4, 1.1%	
Ethnicity		White
White	231, 61.1%	
Black	20, 5.3%	
Asian	96, 25.4%	
Mixed	13, 3.4%	
Other	18, 4.8%	
Income		Retired
<£14999	30, 7.9%	
£15000-£24999	42, 11.1%	
£25000-£34999	31, 8.2%	
£35000-£44999	30, 7.9%	
£45000-£54999	5, 1.3%	
£55000-£64999	5, 1.3%	
£65000-£74999	1, 0.3%	
>£75000	6, 1.6%	
Unemployed	32, 8.5%	
Retired	196, 51.9%	
Education		GCSE or Equivalent
No formal education	60, 15.9%	
GCSE or Equivalent	122, 32.3%	
A-Level or Equivalent	65, 17.2%	
Bachelors Degree or Equivalent	94, 24.9%	
Post-graduate Degree or Equivalent	26, 6.9%	
Other	11, 2.9%	
Clinical Factors		
BMI (kg/m^2)	351, 92.9%	29.4 (29.35 ± 6.17, 14.8-51.0)
HbA_{1c} (%, mmol/mol)	266, 70.4%	7.1%, 54 (7.7% ± 3.9%/60.29 ± 18.82, 4.7-14.4%, 28-134)
Number of antiglycaemics	378, 100%	1 (1.92 ± 0.90, 1-5)
Number of conditions	378, 100%	4 (4.70 ± 3.14, 1-17)

3.5.1.2b Factor & Reliability Analyses

Prerequisite testing for factor analyses provided the following results – a suitable KMO measure of sampling adequacy was obtained at 0.855 (>0.5) and Bartlett's test of sphericity was significant ($\chi 2$=5868.244, p<0.0001). Following confirmation with these results, EFA was conducted using Direct Oblimin rotation. In total, 13 factors were identified with eigenvalues >1 (Table 3.11), which matched a very small inflection point on Factor 13 when reviewing the corresponding scree plot (Figure 3.3)

Table 3.11 – SPUR Factor Eigenvalues

Factor	Eigenvalue[a]	Variance (%)	Cumulative Variance (%)
1	9.301	20.669	20.669
2	3.339	7.419	28.088
3	2.014	4.475	32.563
4	1.814	4.031	36.594
5	1.683	3.740	40.334
6	1.512	3.361	43.695
7	1.463	3.252	46.946
8	1.324	2.941	49.888
9	1.232	2.739	52.626
10	1.189	2.642	55.268
11	1.154	2.564	57.833
12	1.080	2.400	60.233
13	1.008	2.239	62.472

Notes:[a]Factors (14-45) with eigenvalues <1 are excluded from Table 3.12

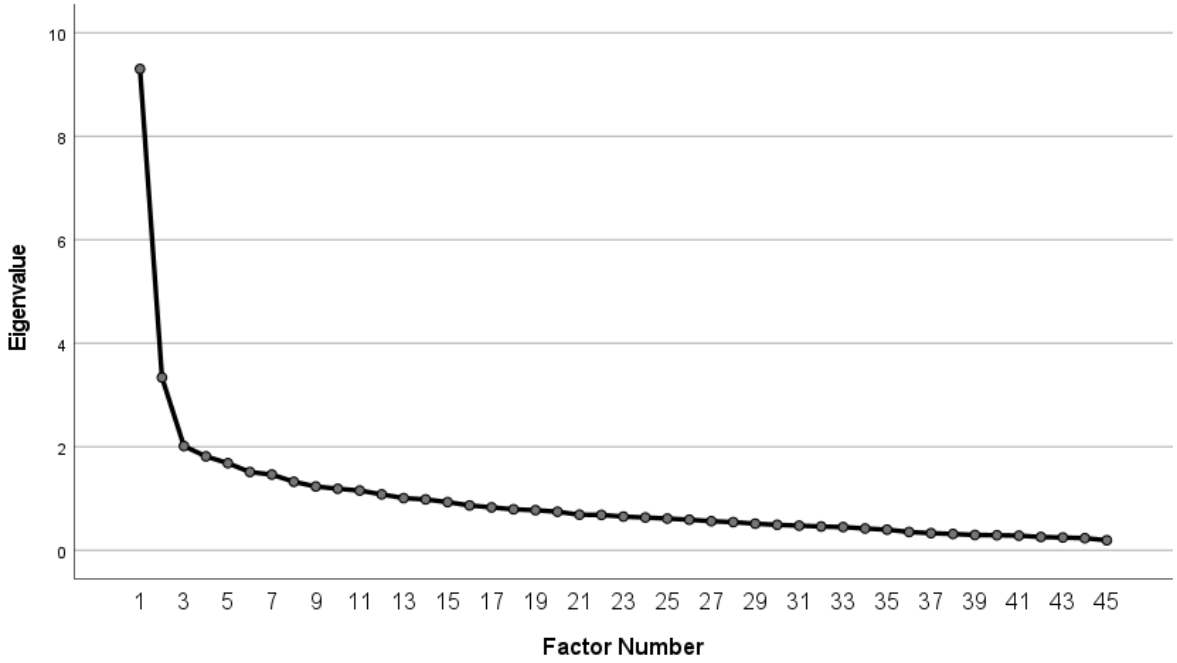


Figure 3.3 – SPUR Scree Plot

The 13-factor solution for SPUR explained 62.47% of the variance however, six items demonstrated factor loadings <0.32 (Table 3.12). The items covered all four domains of the SPUR model, however items within the Rational domain were the most prevalent (50.0%, n=3/6). Further Monte Carlo parallel analysis did not support the retention of a 13-factor solution. To find a suitable solution, iterative scale reduction was conducted by continually trimming items with loadings <0.32, which included the removal of the six items (Table 3.12) from the initial 13-factor solution. An additional scale reduction using the same method removed five items to produce a 34-item scale. The new iteration produced a 10-factor solution (n=34 items, KMO=0.868, $\chi 2$=4679.905, p<0.0001) that explained 64.23% of the variance.

Table 3.12 – Items with Factor Loadings <0.3 (SPUR 13-Factor Solution)

Item No	Statement	Domain
3	I would be interested in knowing if others with diabetes follow their treatment plan.	Social
4	I think that people with diabetes generally follow their doctors' prescription exactly.	Psychological
10	Sometimes my diabetes seems unreal to me.	Rational
18	I can easily pay for my treatment.	Usage
42	My diabetes keeps me from doing things I want to do.	Rational
44	Non-traditional treatments could replace some of my medications.	Rational

Having identified a complete model with adequate factor loadings, estimates of internal consistency were reported using Cronbach's alpha (α). The 34-item scale reported a strong estimate of internal consistency (α>0.8) with α=0.887. Individual item-total correlations (ITCs) provide an overview of how each item corresponds with the overall scale; ITCs <0.3 may be considered as a cut-off for determining potential items for removal from the model to improve overall reliability.[287] The initial review identified five items with ITC <0.3 (Table 3.13). Removal of these items produced a 29-item scale with strong internal consistency (α=0.898). Repetition of the reliability analysis identified a single item with an ITC<0.3 that if removed would marginally improve α to 0.899 (Original Item 15 – 'Sometimes doctors prescribe you treatment you don't really need'). Removal of item 15 produced the 28-item model (α=0.899). Items (n=2) that led to an increase in α scores if removed but with an ITC>0.3 were retained given that α>0.9 may indicate item redundancy.[288]

Table 3.13 – Item-Total Correlations (ITCs) for the 34-item SPUR Model

Item	ITC	Cronbach's Alpha if Item Deleted
Medications are more expensive than they should be.	0.124	0.89
I feel worse if I don't follow my treatment plan.	0.126	0.89
I am worried about the side effects of some medications.	0.189	0.889
I don't like taking medications.	0.247	0.888
Too many doctors don't listen to what patients tell them.	0.271	0.887
My diabetes affects my relationships with those I care about.	0.311	0.886
My treatment affects my sex life.	0.328	0.886
Fighting for my health is my highest priority.	0.331	0.885
Sometimes doctors prescribe treatment you don't really need.	0.337	0.886
I have found ways to deal with my diabetes.	0.352	0.885
I am worried about taking medications.	0.36	0.885
I believe I can stop my treatment for my diabetes when I feel better.	0.374	0.885
Sometimes I don't follow my treatment plan exactly.	0.396	0.884
My diabetes affects my social life.	0.405	0.884
I find it easy to follow my treatment plan when I am not at home.	0.408	0.884
My diabetes is likely to get worse if I don't follow my treatment plan.	0.408	0.884
I will have to take a treatment for my diabetes for the rest of my life.	0.419	0.884
I find it easy to get my treatment for my diabetes.	0.433	0.884
My diabetes should be taken seriously.	0.44	0.884
I am satisfied with the level of information I have about my treatment.	0.449	0.883
I completely understand my diabetes.	0.453	0.883
Medications for my diabetes don't do anything for me.	0.467	0.883
There is no point in taking medications for my diabetes.	0.49	0.883
My treatment helps my diabetes.	0.513	0.883
Following my diabetes treatment plan lets me do the things I want to do.	0.515	0.882
It is essential that I follow my treatment plan.	0.559	0.882
I'm the kind of person who will follow their treatment plan exactly.	0.561	0.881
I am satisfied with the level of information I have about my diabetes.	0.564	0.881
Precisely following doctors' recommendations is the best way for me to stay healthy.	0.568	0.882
I find it easy to manage the different medications I take.	0.608	0.881
I trust the doctors' recommendations.	0.609	0.881
I find it easy to take my medications for my diabetes.	0.61	0.88
I am able to follow my treatment plan.	0.616	0.881
If my doctor recommends that I do something, I do it.	0.632	0.881

Notes: [a]ITC<0.3

EFA was repeated on the 28-item model to evaluate the factorial structure for the abbreviated version of SPUR. The analysis produced a 7-factor solution (n=28 items, KMO=0.889, χ^2=4015.279, p<0.0001) that explained 60.56% of the variance, however, 1-item reported a factor loading <0.32 (Original Item 28 – 'I am worried about taking medications') (See Appendix A). Removal of the item produced a 7-factor solution (n=27 items, KMO=0.889,

χ^2=3941.015, p<0.0001) that explained 61.85% of the variance (Table 3.14). Reliability analysis indicated excellent internal consistency (α=0.900), hence this model, referred to as SPUR-27, with a suitable factorial structure was retained for continued psychometric analysis.

Table 3.14 - SPUR-27 Factor Eigenvalues

Factor	Eigenvalue[a]	Variance (%)	Cumulative Variance (%)
1	8.177	30.285	30.285
2	1.971	7.299	37.585
3	1.627	6.027	43.612
4	1.404	5.200	48.812
5	1.301	4.818	53.629
6	1.166	4.317	57.946
7	1.053	3.900	61.847

[a]Factors (8-27) with eigenvalues <1 are excluded from Table 3.14

For each factor (defined as a subscale), items were aggregated in accordance with the four main SPUR domains from the original 45-item questionnaire (Table 3.15). Item factor loadings, mean scores, and SDs are described in Table 3.15.

Table 3.15 - SPUR-27 Item Content, Factor Loadings and Descriptive Statistics

Item	Factor	Subscale	Original SPUR Domain	Factor Loading	Mean	SD (±)
Precisely following doctors' recommendations is the best way for me to stay healthy.	1	Treatment Motivation	P	0.784	4.20	0.974
I trust the doctors' recommendations.	1		P	0.732	4.21	0.999
If my doctor recommends that I do something, I do it.	1		P	0.546	4.12	1.007
It is essential that I follow my treatment plan.	1		P	0.515	4.36	0.946
Fighting for my health is my highest priority.	1		P	0.467	4.16	1.070
My diabetes affects my social life.[a]	2	Interpersonal Relationships	S	0.728	3.79	1.338
My diabetes affects my relationships with those I care about.[a]	2		S	0.692	3.85	1.347
My treatment affects my sex life.[a]	2		S	0.440	3.67	1.387
There is no point in taking medications for my diabetes.[a]	3	Treatment Consequence	R	0.747	4.23	1.089
Medications for my diabetes don't do anything for me.[a]	3		R	0.632	3.98	1.139
I believe I can stop my treatment for my diabetes when I feel better.[a]	3		R	0.529	3.89	1.277
My diabetes should be taken seriously.	3		R	0.478	4.45	0.969
I will have to take a treatment for my diabetes for the rest of my life.	3		R	0.392	4.18	1.116
My treatment helps my diabetes.	3		R	0.369	4.23	0.897
My diabetes is likely to get worse if I don't follow my treatment plan.	3		R	0.357	4.30	0.971
I am satisfied with the level of information I have about my diabetes.	4	Knowledge Satisfaction	R	0.917	3.94	1.169
I completely understand my diabetes.	4		R	0.657	3.57	1.271
I am satisfied with the level of information I have about my treatment.	4		R	0.594	3.91	1.183
Sometimes I don't follow my treatment plan exactly.[a]	5	Adherence Behaviour	U	0.703	3.32	1.414
I'm the kind of person who will follow their treatment plan exactly.	5		U	0.657	3.88	1.179
I am able to follow my treatment plan.	5		U	0.414	4.22	0.962
I have found ways to deal with my diabetes.	6	Treatment Control	R	0.552	3.83	1.136
Following my diabetes treatment plan lets me do the things I want to do.	6		R	0.455	3.75	1.051
I find it easy to take my medications for my diabetes.	7	Ease of Use & Access	U	0.750	4.14	1.105
I find it easy to manage the different medications I take.	7		U	0.697	4.10	1.099
I find it easy to get my treatment for my diabetes.	7		U	0.544	4.23	1.123
I find it easy to follow my treatment plan when I am not at home.	7		U	0.461	3.49	1.324

Notes:[a]Reverse coded item

In addition to the overall SPUR-27 model, individual subscales (factors) were assessed for estimates of internal consistency in line with validation recommendations (Table 3.16).[186] The α values for each subscale ranged from 0.56 to 0.82, demonstrating adequate to strong internal consistency. ITCs ranged from 0.348 to 0.744 across the seven factors. Inter-factor correlations were significant ($p<0.01$) and ranged from 0.245 to 0.631.

Table 3.16 - Inter-factor Correlations & Internal Consistency Estimates for all Subscales

	Inter-factor Correlations							**IC**
Factors	F1	F2	F3	F4	F5	F6	F7	α
F1 Treatment Motivation (P)[b]	1	.245[a]	.477[a]	.439[a]	.631[a]	.444[a]	.532[a]	0.82
F2 Interpersonal Relationships (S)		1	.268[a]	.288[a]	.263[a]	.293[a]	.424[a]	0.70
F3 Treatment Consequence (R)			1	.425[a]	.510[a]	.414[a]	.448[a]	0.77
F4 Knowledge Satisfaction (R)				1	.422[a]	.348[a]	.472[a]	0.76
F5 Adherence Behaviour (U)					1	.342[a]	.512[a]	0.56
F6 Treatment Control (R)						1	.416[a]	0.65
F7 Ease of use/access (U)							1	0.79

Notes:[a]$p<0.01$, [b]Letters associated with each factor indicate the original SPUR domain (Social, Psychological, Usage, and Rational)

Abbreviations: IC, internal consistency

3.5.1.2c SPUR-27 Item Distribution

Scores for each of the 45 items in the original SPUR model were assigned on a scale from 1 to 5, with a higher score indicating a greater likelihood of adherence. Most items demonstrated a left-skewed distribution, with a range of scores from 2.73 to 4.45 and a total mean score of 3.72 ± 0.07. None of the items that demonstrated a right-skewed distribution (n=3) were retained for the SPUR-27 model after iterative reductions to items through EFA and reliability analyses. Nearly 89% of the items (88.9%, n=40/45) had mean scores between 3.10 and 4.45, indicating similar effects on answer responses from participants. Overall, SPUR-27 scores ranged from 32.40% to 98.21% (mean±SD=77.08±12.05) with 44.7% (n=169/378) scoring ≥80% (Table 3.17). Individual factor mean scores ranged from 73.16% to 84.16%. Individual factor scores demonstrated a range of up to 100.0%, indicating that at least one individual had provided responses to items to achieve a maximum score for that specific subscale. Floor or ceiling effects occur when a proportion of respondents score the highest or lowest score, which may indicate that a model may have a poor capacity for discriminating between individuals at each end of the measure.[297] While the range for six of the subscales indicate a maximum score range was observed within the sample, this did not translate into the overall SPUR-27 score, hence no ceiling effect was observed. Similarly, the minimum score of 20.0% was observed for four subscales, however this was not reflected as a floor effect for the overall SPUR-27 score.

Table 3.17 – SPUR-27/Subscale Score

Overall Model/Subscale	Mean Score (% ± SD)	Range (%)	
		Min	Max
SPUR-27	77.08 ± 12.05	32.40	98.21
F1 – Treatment Motivation (P)[a]	84.16 ± 15.22	36.00	100.00
F2 – Interpersonal Relationships (S)	75.42 ± 21.41	20.00	100.00
F3 – Treatment Consequence (R)	73.16 ± 12.19	30.00	87.50
F4 – Knowledge Satisfaction (R)	76.07 ± 20.46	20.00	100.00
F5 – Adherence Behaviours (U)	75.34 ± 17.23	26.67	100.00
F6 – Treatment Control (R)	75.71 ± 18.43	20.00	100.00
F7 – Ease of Use/Access (U)	79.71 ± 17.81	20.00	100.00

Notes: [a]Letters associated with each factor indicate the original SPUR domain (Social, Psychological, Usage, and Rational)

3.5.1.2d Construct, Convergent, & Discriminant Validity

Average factor loadings for individual SPUR-27 subscales (F1-F7) are reported in Table 3.18. The subscale with the lowest average factor loading (F6/Control) also observed the lowest number of items (n=2), however the average factor loading was moderate (0.5) and therefore acceptable.[298]

Table 3.18 – SPUR-27 Subscale Factor Loading

Subscale	Average Factor Loading
F1 – Treatment Motivation (P)[a]	0.609
F2 – Interpersonal Relationships (S)	0.620
F3 – Treatment Consequence (R)	0.501
F4 – Knowledge Satisfaction (R)	0.722
F5 – Adherence Behaviours (U)	0.591
F6 – Treatment Control (R)	0.504
F7 – Ease of Use/Access (U)	0.613

Notes: [a]Letters associated with each factor indicate the original SPUR domain (Social, Psychological, Usage, and Rational)

Convergent validity was assessed by comparing SPUR with other PROMs. Spearman's rank correlation coefficients (ρ) are reported given that the results were non-normally distributed (Table 3.19). SPUR-27 demonstrated significant (p<0.01) correlations with the included PROMs as a total model, as well as with individual subscales, providing evidence of convergent validity. When assessing discriminant validity, Factor 1 (SPUR-27), which is reflective of the original Psychological SPUR domain, exhibited the strongest correlation with the BeMQ-S. This was an anomalous result given that BeMQ-S, which contains items relating to necessity and concerns, would have been expected to be most predictive of the Rational domain for the SPUR model. Conversely, Factors 2-7 (SPUR-27) did observe the strongest correlations with their expected comparative PROM as hypothesised prior to the validation analysis. Moreover, all individual SPUR subscales were significantly correlated with the measure of treatment satisfaction (DTSQ), with a strong positive correlation (ρ>0.6) observed for the overall SPUR-27 score (ρ=0.647). Notably, DTSQ was only included as a pseudo-comparator of treatment satisfaction and not to support the convergent validity analysis – See Section 3.6.3. The evidence of convergent validity across all subscales and domains against the comparator PROMs provides an early indication of construct validity for SPUR as a holistic model of MA.

Table 3.19 – Spearman's Rank Correlation Coefficient for Included PROMs *vs* SPUR-27

PROM	DTSQ	BeMQ-General (P)	MARS (U)	BeMQ-Specific (R)
SPUR (27-items)	0.647[a]	0.409[a]	0.547[a]	0.639[a]
F2 – Interpersonal Relationships (S)[c]	0.346[ab]	0.213[a]	0.250[a]	0.297[a]
F1 – Treatment Motivation (P)	0.575[a]	0.287[a]	0.328[a]	0.428[ab]
F5 – Adherence Behaviours (U)	0.504[a]	0.426[a]	0.499[ab]	0.396[a]
F7 – Ease of Use/Access (U)	0.544[a]	0.370[a]	0.417[ab]	0.410[a]
F3 – Treatment Consequence (R)	0.448[a]	0.297[a]	0.426[a]	0.612[ab]
F4 – Knowledge Satisfaction (R)	0.503[a]	0.298[a]	0.361[a]	0.441[ab]
F6 – Treatment Control (R)	0.376[a]	0.136	0.378	0.381[ab]

Notes:[a]p<0.01;[b]Highest ρ for each SPUR subscale *vs* a comparator PROM; [c]Letters associated with each factor indicate the original SPUR domain (Social, Psychological, Usage, and Rational)

3.5.1.2e SPUR-27 Concurrent Validity

Concurrent validity, often defined as the comparison with a novel PROM against a suitable gold standard, was evaluated using two objective MA measures, MPR and HbA_{1c}. The overall SPUR-27 scores were significantly and inversely correlated with HbA_{1c} ($\rho=-0.143$, $p<0.05$) and positively correlated with MPR ($\rho=0.228$, $p<0.01$) as demonstrated in Table 3.20.

Table 3.20 - Spearman's Rank Correlation Coefficient for Objective Measure *vs* SPUR

	HbA_{1c}	**MPR**
SPUR (27-items)	-0.143[a]	0.228[b]
F1 – Treatment Motivation (P)	-0.035	0.122[a]
F2 – Interpersonal Relationships (S)	-0.149[a]	0.123[a]
F3 – Treatment Consequence (R)	-0.027	0.168[a]
F4 – Knowledge Satisfaction (R)	-0.008	0.121[a]
F5 – Adherence Behaviours (U)	-0.211[**b**]	0.161[b]
F6 – Treatment Control (R)	-0.084	0.215[**b**]
F7 – Ease of Use/Access (U)	-0.142[a]	0.209[b]
Comparator PROMs		
BeMQ-General	-0.135[a]	0.076
BeMQ-Specific	-0.003	0.157[b]
DTSQ	-0.104	0.160[b]
MARS	-0.089	0.209[b]

Notes:[a]$p<0.05$;[b]$p<0.01$

When analysing individual subscales, significant inverse correlations were observed between HbA_{1c} and Factor 5 ($r=-0.211$, $p<0.01$), Factor 2 ($r=-0.149$, $p<0.05$), and Factor 7 ($r=-0.142$, $p<0.05$), which represented subscales for Social and Usage domains from the original SPUR model. Weak positive significant correlations were observed between MPR and all subscales (0.121–0.215). Only BeMQ-G demonstrated a weak significant inverse correlation with HbA_{1c} ($\rho=0.135$, $p<0.05$), whereas BeMQ-S, DTSQ, and MARS demonstrated week significant ($p<0.01$) positive correlations with MPR ($\rho=0.157$-0.209). Further evidence of

concurrent and discriminant validity was sought by comparing groups of participants based on glycaemic control and MPR scores. SPUR-27 was able to distinguish between patients with poor glycaemic control (HbA_{1c}>7.0, n=161/266, 60.5%) *vs* optimal glycaemic control (HbA_{1c}≤7.0, n=105/266, 39.5%), with significantly different total mean SPUR-27 scores for each respective cohort (77.6% *vs* 80.5%, p<0.05). A similar result was observed when comparing mean SPUR-27 scores for patients with low MPR adherence (MPR<80%, n=68/378, 18.0%) and high MPR adherence (MPR≥80%, n=310/378, 82.0%) (73.3% *vs* 77.9%, p<0.01). Excluding the DTSQ, none of the comparator PROMs demonstrated significant discriminant validity between cohorts based on glycaemic control or MPR. Furthermore, the DTSQ was only able to distinguish a significant difference (p<0.05) in cohorts based on glycaemic control, not MPR scores. The SPUR-27 model therefore provided strong evidence of concurrent and discriminant validity.

3.5.1.2f SPUR-27 Known Group Validity

Significant positive associations were observed between SPUR-27 scores and socio-demographic variables including participants' age (ρ=0.354, p<0.01) and income (ρ=0.303, p<0.01), providing partial support of the initial hypothesis for known-group validity in this study. Moreover, BMI (ρ=-0.163, p<0.01) and the number of antiglycaemic agents prescribed (ρ=-0.139, p<0.05) were negatively correlated with SPUR-27 scores. Surprisingly, the number of comorbidities was positively correlated with SPUR-27 scores (ρ=0.246, p<0.01), contrary to the initial hypothesis. There was no significant difference in SPUR-27 mean scores by reported gender (p=0.84, CI 95% -2.23, 2.75, Cohen's d=0.02). The largest difference in SPUR-27 mean score by ethnicity was observed between white (n=231, 80.83 ± 0.77) and Black (n=20, 73.94 ± 2.62) participants, however this finding was not significant (p=0.18, CI 95% -1.13, 12.11, Glass's Δ=0.40). However, in terms of the impact of

recruitment setting, community participants had significantly lower SPUR-27 mean scores than those in the secondary-care arm (73.15 *vs* 80.58, $p<0.0001$, CI 95% 5.07, 9.78, Glass's $\Delta=0.65$), indicating lower self-reported MA. Additionally, a significant difference in HbA_{1c} mean scores was observed when comparing community (n=70/266, 7.3%, 56.34 ± 11.00mmol/mol) and secondary-care participants (n=196/266, 7.8%, 61.69 ± 19.89mmol/mol) ($p<0.01$, CI 95% 1.97, 9.60, Glass's $\Delta=0.32$).

3.5.1.2g Test-Retest Reliability

To determine this element of reliability, it was intended that a sub-sample of each study arm would be recruited at T0 and T6-months to recomplete the SPUR tool. By comparing the results at both intervals, one could infer a value of score consistency across the designated time period. Unfortunately, test-retesting was not achieved for either arm of VMATT2. During the study launch and recruitment period, the Covid-19 pandemic occurred that resulted in a change to recruitment procedures. It was agreed between the research teams at both Kingston University and Kingston Hospital, in addition to CPs involved in recruitment, that the benefit of retesting, which include bringing participants back to either a community pharmacy or outpatient hospital setting, was outweighed by the potential risk of additional Covid-19 exposure for study participants. Therefore, test-retest reliability of the SPUR model was not established during the PhD.

3.6 Discussion

The results of this study demonstrate the outcomes of a bespoke stepwise approach to produce early evidence of validity for a holistic PROM with the support of international methodologies and previous validation studies. Furthermore, this work in particular highlights the complex nature of evaluating a PROM that comprises several domains of

behaviour, in addition to the impact of sociological phenomena such as the Covid-19 pandemic on study development, recruitment, and delivery.

3.6.1 An Iterative Approach to Factor & Reliability Analyses

An objective of this work was to explore the psychometric properties of SPUR as a multidimensional PROM for MA in T2D, and to evaluate the association between the SPUR model and various socio-clinical factors linked to MA. The initial analyses involved repeated factor and reliability testing using the original SPUR tool to determine a suitable model for further psychometric analysis. Following the analyses, a refined and more concise version of SPUR, known as SPUR-27, was developed. The results indicate that the early psychometric properties of SPUR-27 model are promising as a PROM of MA in this population with significant relationships between SPUR-27 outcomes and socio-clinical factors of interest.

EFA, compared to CFA, is of particular use as a data-driven technique to evaluate the underlying structure of a PROM during early development.[299] The COSMIN criteria definitions include 'adequate' and 'very good' for EFA and CFA, respectively, as two approaches to CTT.[186] However, CFA is typically applied for validation of pre-specified models with clear relationships between the observed variables and the underlying factors.[300] VMATT2[278] was the first study to explore the psychometric properties of SPUR, hence EFA was conducted as the preliminary method to explore the structure of the overall SPUR model. SPUR-27 was established using an iterative process of model refinement through EFA in addition to reliability testing with repeated trimming of items with neither sufficient factor loadings (<0.32) nor adequate ITCs (<0.3).[287]

Determination of factorial structure in multidimensional models is particularly critical given the potential complexity associated with interpreting their results where different subscales may have their own scoring methodology and relevance in clinical practice.[301] Typically EFA

employs the use of scree plots of eigenvalues >1 as means of identifying suitable factors for retention within a model. However, methods such as MCPA, which involves the comparison of eigenvalues obtained from the data to those obtained from randomly generated datasets of the same size, can prove to be a superior approach that dramatically improves the accuracy and reliability of results.[285] All three methods were applied to identify the 7-factor solution with suitable subscales that aggregated within all four domains of the original SPUR model and that were reflective of those domains. Acceptable factor loadings were observed across the entire model. The SPUR-27 factors were found to correspond with seven of the 13 hypothesized drivers of MA in each major domain, as previously identified by Dolgin.[179] Compared to the original SPUR model, SPUR-27 reported high internal consistency (α=0.900) with fewer total items.[288] Item reduction can therefore provide benefits to not only factorial stability and reliability, but also PROM interpretability.[186] Simply put, more concise tools may require from patients less time and investment to complete and from clinicians, less time and effort to implement and interpret. Evidence of concerns specifically related to SPUR interpretability and acceptability were identified in terms of the length of the PROM from both the patients and HCP pilot studies. Therefore, while both pilots provided early evidence of face and content validity, additional testing through VMATT2 has helped to address early concerns with adjustments to the overall length of the model.

3.6.2 SPUR-27 Scores & Cohort Adherence

Mean total and individual factor scores for SPUR-27 were evaluated. Sample adherence for SPUR-27 was assessed using a ≥80% cut-off, which resulted in a reported adherence of 44.7% (n=169/378) across the cohort. A similar finding was reported by Farr *et al*[256] in one of the largest cohort studies (n=238,372) of long-term MA in T2D, which identified an adherence range of 36.7-47.3% depending on the type of T2D medications prescribed. The

proportion of the VMATT2 cohort with available data defined as adherent using HbA_{1c} was 39.9% (n=106/266). An observational study of glycaemic control among patients with T2D (n=2403) between 1999-2010 conducted by Wong *et al*[302] found that only 45.5% (n=1093) achieved suggested HbA_{1c} targets. Hence, this provides preliminary evidence of compatibility between both measures.

Assessment of the cohort using MPR data demonstrated that 82.0% of participants were adherent (MPR≥80%, n=310/378), which was not unexpected as MPR tends to overestimate adherence.[158] The tendency of MPR over-estimation is in part due to the inability of the measure to meaningfully capture medication-taking behaviour or medicines consumption.[303] Patients may fail to take their medicines, however these data may not be reported during the assessment interval without further intervention from a researcher or HCP, such as a pharmacist, that may explore individual instances of poor MA.

Though not defined in the methods as an outcome of interest, anecdotal reports of CPs' experience during the delivery of the VMATT2 study may provide some insight into the disparity in MA reports. The study's pharmacists reported less contact with patients during recruitment due to the Covid-19 pandemic, which led to medicines being delivered to patients' homes without face-to-face engagement. Although this approach was taken to protect both patients and CP teams from Covid-19, this may have inadvertently resulted in a reduced capacity for conversations or interventions related to MA. This impact on service delivery has previously been described by Hayden and Parkin[304] in their review of challenges faced by both patients and CPs during the Covid-19 pandemic. The review emphasised the particular impact on vulnerable groups e.g., older patients or those requiring continuity in care such as individuals diagnosed with chronic conditions. For patients with T2D during the pandemic, reduced support from pharmacy teams with their medicines may be directly

reflected through poorer glycaemic control (higher HbA_{1c}). However, despite this reduction in contact with patients, medicines were still dispensed and could therefore contribute to an increased MPR score when assessing pharmacy record data. Hence, these data may have been exaggerated and not a true reflection of MA behaviour among the cohort. The impact of Covid-19 on medicines use and access to diabetes care has been difficult to quantify, however the literature suggests that people with T2D have been disproportionately affected by the pandemic, both within the UK and internationally.[305,306] With this in mind, one must take a cautious approach when considering the interpretability and generalisability of these results to the broader population of individuals living with T2D either before, or even after the Covid-19 pandemic. This is particularly noteworthy, considering that although data were collected pre- and post-Covid in terms of lockdowns, the initial sample (n=<15) meant that analyses were not powered nor large enough to justify any between-group differences that may have been evaluated. Nevertheless, the comparability of HbA_{1c} and SPUR MA scores in this study to more widely reported observational data with large cohorts are encouraging.[256,302]

3.6.3 Multidimensional Validity

Previous studies and criteria for evaluating the measurement properties of multidimensional PROMs have included an assessment of individual subscales as a means to explore construct validity.[186,307] Ideally, this assessment should include hypothesis testing whereby PROM scores align with predicted relationships, such as internal relationships between constructs, relationships with scores of other instruments (comparative PROMs), or differences between relevant groups (such as inter-group analyses based on socio-clinical data relevant to the construct being measured), based on the assumption that the PROM accurately measures the intended construct.[186] In the absence of a gold standard holistic PROM of MA, three

additional PROMs, with one containing two specifically relevant subscales (BeMQ-G/S), were chosen as comparators. As per the recommendation of the literature, the revised SPUR-27 demonstrated fair (≥0.3-0.59) to moderate (≥0.6-0.79) correlations for total scores and individual factors when compared to the corresponding PROM providing evidence of convergent validity and overall construct validity.[308] For example, as hypothesised Factor 5 (Adherence Behaviours), which contains three items originally within the Usage domain, correlated most strongly with MARS that was included as a PROM to reflect the original SPUR Usage domain.[308]

Conversely, Factor 1 (Treatment Motivation) was identified as an exception to the hypothesis testing. The five items within this subscale were reflective of the original Psychological domain for SPUR. Therefore, it was expected that this subscale would correlate most strongly with BeMQ-General. However, it had the weakest correlation with BeMQ-General, but acceptably significantly correlated with SPUR-27 (>0.4). Interestingly, Factor 1 showed the strongest correlation with the DTSQ score, suggesting that overall treatment satisfaction may be more impactful on overall treatment motivation than the physician-patient relationship alone in determining MA. Notably, both treatment satisfaction and the physician-patient relationship can have a synergistic impact on improving MA in T2D, hence there may be some overlap between these drivers of behaviour.[309] This finding highlights one critical consideration for the overall SPUR model. While the comparator PROMs in almost all cases correlated most strongly with their relevant factor/domain, providing evidence of construct validity, each factor was predominantly and significantly correlated to some degree with most comparators. Hence, while individual subscales may measure one construct, these overlaps suggest an underpinning latent factor for the entire model, which is hypothesised as

adherence behaviour. Further evidence of this latent trait has been supported by De Bock *et al*[310] with the application of Rasch modelling that supports this hypothesis.

3.6.4 Known-Group Validity & Clinical Relevance

In addition to hypothesis testing conducted through convergent validity of SPUR-27 and other PROMs, a similar model was applied to explore known-group validity using socio-clinical characteristics of the study sample. Expected associations between MA and factor including age, income, BMI, and the number of antiglycemic medications was established. However, in contrast the number of comorbidities observed a positive correlation to MA. This finding was counter-intuitive to initial hypotheses relating to multimorbidity, which as discussed in Chapter 1 is often associated with poorer clinical outcomes related to non-adherence. Although unexpected, similar findings have been reported previously by Briesacher *et al*.[311] One possible explanation may be the increased healthcare utilisation of those diagnosed with chronic conditions and/or multimorbidity more specifically. A 2021 SR exploring multimorbidity and healthcare utilisation in the UK identified an increase in service access for primary care, secondary care, and emergency departments, with the latter two being significantly associated with hospitalisation.[312] Unfortunately, this review does not comment on utilisation during the Covid-19 pandemic, however McGreevy *et al*[313] provide useful insights that may be applicable to results of the VMATT2 study. The authors describe the prioritisation of older patients for primary care services during the pandemic, who were also more likely to present with multimorbidity or "vulnerable" long-term conditions, such as T2D. Hence, while individuals without multimorbidity observed a 7% reduction in primary care access, those considered more at risk were more likely to engage with these services. This engagement may have inadvertently been an opportunity to discuss MA and potential interventions, particularly for individuals with T2D that was associated with significantly

poorer Covid-19 related outcomes that resulted in increased public health messaging for this population during the pandemic.[314,315]

The SPUR-27 measure was the only tool that identified differences in adherence patterns for both HbA_{1c} and MPR measures. While the correlations reported by SPUR-27 were weak (<0.3), it was the only measure in addition to the BeMQ-General that produced significant results. SPUR-27 also demonstrated the highest correlation with HbA_{1c} and MPR among all the included PROMs. A potential explanation for this finding is that the pandemic may have reduced the frequency of HbA_{1c} testing. In their evaluation of HbA_{1c} uptake during the pandemic, Holland *et al*[316] reported an 82-88% reduction in testing following the first March 2020 lockdown in England. Even small delays to regular HbA_{1c} testing may have significant clinical implications given that three-monthly interval testing has previously been associated with a 3.8% reduction in HbA_{1c} compared with a 1.5% increase when monitoring is conducted annually.[316] This reduction in testing may have therefore resulted in disparities with perceived self-management of self-care activities such as diet, exercise, and critically for this discussion, MA. Nonetheless, it is encouraging that SPUR-27 was still able to detect significant variations in HbA_{1c} compared to the other previously validated PROMs whereby a stronger relationship with glycaemic control would have perhaps been expected.

From this perspective, factors outside of MA may have played a more important role in changes to HbA_{1c} than anticipated. For example, repeated lockdowns had a consistently negative impact on diet and exercise uptake in individuals diagnosed with T2D.[317] Patients who continue to take their medication regularly but do not maintain their usual self-care routine may still experience suboptimal HbA_{1c} levels, which may not fully correlate with self-reported MA, as partly evidenced by the PROM results observed in this study. An important comment must also be made in relation to social desirability bias and discrepancies

in self-reported HbA_{1c} that were not fully explored during VMATT2. As an example, the community-arm methodology involved participants self-reporting their most recent HbA_{1c} result from memory. The likelihood of an error in reporting in the community pharmacy setting is much higher than that of HbA_{1c} reporting in the hospital arm, where it was directly extracted from the patients' medical record. While a significant difference in HbA_{1c} between both arms was observed during VMATT2, it is not unexpected that those in a hospital setting would be expected to report poorer glycaemic control. However, irrespective of this finding, further work should be conducted to explore the true correlation between self-reported HbA_{1c} and self-reported MA, using methods as SPUR-27, to provide more context to the relationship between both measures.

3.6.5 Limitations

The lack of test-retest reliability is a limitation for the VMATT2 study. These data were unavailable due to the pandemic preventing a suitably safe follow-up with participants. While re-testing with sub-samples from both the community and hospital cohorts were planned as part of the original methodology, a benefit-to-risk ratio directed the decision to exclude this analysis. While other reliability results were encouraging, future work should look to address this to build a more comprehensive model of SPUR validity. Moreover, while a PPI approach was embedded as part of the pilot development, utilising a talk-aloud pilot methodology may have provided additional insights about how participants interface with the SPUR model prior to the launch of the study. The over-representation of male participants in this study (almost 60% of the total sample) means that assertions of evidence for validity are based on a predominantly male sample and may not consider gender-specific biases to certain items. However, no statistically significant difference was observed when comparing SPUR-27 mean adherence scores by gender as part of the known-group validity testing. In terms of the

factorial analysis, the benefits of MCPA have been described throughout the chapter, however it should be noted that caution is required with this method due to the risk of over-factoring models. It should be emphasised that this study included only one specific population of individuals diagnosed with T2D from two different settings that were localised to Southwest London. Therefore, without replicable models and data from additional populations, it is important that these findings are not considered as definitely conclusive of SPUR-27 validity in all individuals diagnosed with T2D. In fact, the notion of iterative and on-going evaluation of PROMs to build on previous evidence of validity is a critical principle applied throughout this thesis in line with COSMIN guidance and recommendations from the wider PROM research community.[186,318,319] Continued engagement with SPUR-27 validity analyses is required to ensure that these and future results are truly meaningful for individuals diagnosed with T2D as we look to address and support MA and broader health outcomes.

3.7 Conclusion

This Chapter has described several strengths that support the primary outcome of providing early evidence of the psychometric properties of the SPUR-27 model. Firstly, the study integrated several comparative PROM models to provide evidence of convergent and construct validity for this multidimensional model of complex MA behaviour. Secondly, VMATT2 successfully implemented two objective MA measures currently used in clinical practice to demonstrate concurrent validity of SPUR-27. In particular, the integration of HbA_{1c} within the analyses has provided an interesting perspective and discussion on glycaemic control among participants with poor MA in a unique period of time with the Covid-19 pandemic that has had a disproportionate negative impact of those diagnosed with T2D. Thirdly, iterative EFA and reliability analyses produced a more concise tool, SPUR-27, which provided early evidence of psychometric properties for this sample population in

addition to addressing concerns identified in earlier pilot studies regarding the length of the original 45-item model. Moreover, to my knowledge this is the first study to demonstrate the psychometric properties of a holistic PROM for MA in T2D that encompasses four major domains of adherence behaviour within a single tool.

This initial evaluation of psychometric properties for SPUR-27 provides a useful foundation for exploring validity in additional chronic conditions, which this thesis will look to address in Chapter 4. Furthermore, the strong association between SPUR-27 and a clinical outcome measure such as HbA_{1c} warrants additional investigation of the PROM's correlation with other relevant health outcomes to develop further evidence of real-world applications for SPUR-27 that will be discussed in Chapter 5.

Chapter 4: SPUR: Psychometric properties of a patient-reported outcome measure of medication adherence in Chronic Obstructive Pulmonary Disease

4.1 Introduction

As described in Chapter 1, COPD is a chronic respiratory condition that is characterised by a progressive and irreversible decline in lung function. The disease is typically associated with exposure to substances that can induce alveolar abnormalities as a result of inflammation, such as tobacco smoke, air pollution, and occupational dust and chemicals.[320–322] People living with COPD often experience episodic breathlessness, coughing, and abnormal mucus secretion, which can significantly impact their quality of life.[323] Unfortunately, COPD is becoming an increasingly common respiratory condition, with a reported 44.2% increase in global prevalence between 1990 and 2017.[324,325] This increase is largely attributed to the combination of ageing populations with a high prevalence of smoking and exposure to air pollution worldwide; although notably low-middle income countries (LMICs) are the most disproportionately affected.[320,326] Global mortality rates have also significantly increased in this period, with 3.2 million COPD deaths recorded in 2017, accounting for 5% of all deaths worldwide.[325] This represents an 11.6% rise in mortality since 1990, making COPD the fourth leading cause of death globally.[90,324]

4.1.1 Exploring the Burden of COPD

A recent large-scale observational study conducted in Spain evaluated the all-cause mortality rate of COPD patients (n=59,369) compared to the general population of adults over the age of 40 (n=1,219,749).[327] The results revealed that the mortality rate for COPD patients was 5.6%, significantly higher than the 1% observed in the general population. Causes of mortality are often variable depending on the severity of COPD and other comorbidities.[328]. The risks of mortality and multimorbidity can play an important role in HRQoL for patients

living with COPD. Moreover, the severity of COPD has been directly linked to poorer HRQoL outcomes, even in cases of mild disease.[323] HRQoL factors may include limitations to social interactions with friends and family, persistent breathlessness leading to reduced exercise tolerance, as well as sleep disturbance affecting both everyday personal and professional activities. [323,329–331] Based on these factors alone, it is unsurprising that psychological comorbidities such as depression and anxiety are highly prevalent among people living with COPD.[332] A longitudinal population study of UK primary care patients (n=35,722) identified an incidence rate of 16.2 per 1000 patients for new-onset depression in individuals with COPD, compared to 9.4 in those without a COPD diagnosis.[333] Patients diagnosed with severe COPD were also found to be twice as likely to report a diagnosis of depression (OR 2.01; 95% CI 1.45, 2.78). This exposure to increased risk of mortality, multimorbidity, psychological distress and significant effects on daily HRQoL highlights the potential social and clinical complexities of living with COPD, particularly without appropriate management of the condition. Effective COPD treatment requires a comprehensive patient-centred approach that includes interventions such as smoking cessation, pharmacological therapy, pulmonary rehabilitation, preventive measures such as vaccines and reduced exposure to environmental triggers.[334,335]

4.1.2 Adherence in COPD

Inhalers are an essential component in the pharmacological treatment of COPD, and as described in Chapter 1, they are the backbone of all treatment stratifications when classified using the GOLD framework.[334] However, improper use e.g., poor inhaler technique, or non-adherence to inhaled therapies can increase the risk of hospitalisation. [336,337] This is often due to COPD exacerbation, which in turn is associated with worsening mortality. In addition to poor adherence, hospitalisation risk was also found to be predicted by other socio-clinical

factors including depression, comorbidity, and a history of hospital admissions. These findings highlight the somewhat cyclical and interrelated nature of socio-clinical behaviours and outcomes that relate to COPD. For example, psychological comorbidities and COPD symptom severity have been shown to negatively impact respiratory pharmacotherapy MA.[338,339] Hence, when measuring MA, one must consider holistically the psychological risks, daily QoL, experience of multimorbidity, and previous use of healthcare services among people living with COPD that paint an incredibly unique, complex, and yet insightful picture of a patient's behaviour.

As described by Kwasnicka *et al*,[340] 'motivation to avoid negative health consequences is hypothesised to be insufficient to maintain preventive behaviour'. This hypothesis may be particularly true for those with COPD where poor adherence to inhalers is directly attributed to exacerbations.[341] In turn, COPD exacerbations contribute to higher rates of hospitalisation, increased lengths of stay, significant health economic costs, and a disproportionate risk of mortality.[341–343] Yet despite these risks and evidence that good MA (defined using a dose-count measure on inhalers with a cut-off of ≥80%) can reduce the risk of severe exacerbations by up to 44% (OR 0.56; CI 0.48, 0.65), poor adherence still persists.[344] Importantly, this observed risk reduction was true independently of factors such as treatment type, sex, age, smoking status, BMI, prior exacerbation and airflow limitation (defined using FEV_1). However, while the well-known 2011 WHO papers cites that only 50% of individuals living with a chronic condition are adherent to their medicines, even lower rates (<40%) are observed among patients living with COPD, with reports as low as 7%.[141,345–348]

Much like the general behavioural determinants described in Chapter 1 and those specifically relevant to T2D in Chapter 3, patients living with COPD experience a wide array of factors that contribute to non-adherence including: psychosocial factors, such as forgetfulness,

inadequate inhaler technique, limited recognition of therapeutic benefits, poor patient-clinician relationships, and beliefs about medicines and their adverse effects.[347,349,350] One hypothesises that comprehensive methods to identify the most predominant drivers and/or barriers of MA, such as SPUR, can support the development and delivery of tailored interventions. For example, item 26 of SPUR-27 explores ease of medicines use. One might also predict that those struggling with inhaler technique would report lower scores for this item. In isolation, identifying poor inhaler technique as a means for intervention may be incredibly meaningful given that a cohort study (n=1664) by Melani *et al*[351] identified up to 50% of patients misusing their inhalers. Incorrect inhaler technique was a significant (p<0.0001) predictor of hospitalisation (OR 1.47 ± 0.17), exacerbations (OR 1.62 ± 0.20), and rescue pack use (steroid and/or antibiotic prescriptions) (OR 1.50 ± 0.15). Identifying even one facet of behaviour for intervention could have significant health outcome and economic benefits, hence one can surmise that a holistic model for assessing behavioural determinants in tandem may offer even greater benefits.

4.1.3 Rationale & Building on the Foundations of VMATT2

The VMATT2 study provided early evidence of psychometric properties of SPUR as a holistic model of MA and related behaviour, with a specific focus on T2D.[278] Chapter 3 outlined a bespoke validation framework using methodologies adapted from COSMIN, FDA PRO guidance, and other relevant validation studies and protocols.[186,187,266,267,269,270] However, evidence of validity is neither static nor applicable to multiple PROM models without further evaluation and iterative testing.[186,318,319] While the SPUR model was designed as a general model for any chronic condition, a step-wise approach to demonstrating validation in condition specific cohorts was implemented. This method was taken with a view to sequentially explore cross-cultural validity with new patient populations as data were

continually added to the evidence-base for the overall SPUR model before future meta-analyses with significantly large data sets could be conducted. Specifically, cross-cultural validity assesses the degree to which the construct being measured is similar across cultures/populations, and whether the measure is interpreted in the same way. One might assume that given the overlap in behavioural determinants described for COPD and T2D in the above sections and Chapter 3, respectively, that cross-cultural validity for SPUR would be implied. However, in the absence of larger general data sets for SPUR, the novelty of the model's holistic nature, and previous evidence of the impact from external sociological phenomena on study results (specifically referencing Covid-19 on VMATT2), this assumption is both risky and fails to adhere to recommendations for iterative model development that underpin this thesis.[186,318,319]

4.1.4 Aims & Objectives

This study aimed to provide evidence of the psychometric properties of SPUR in a novel population of patients diagnosed with COPD. The study also aimed to implement facets of the previously developed bespoke validation framework to support cross-cultural validity of the model with extensive hypothesis testing. The objectives of this chapter are:

- To evaluate the psychometric properties of SPUR in patients diagnosed with COPD from a hospital setting
- To explore the associations between SPUR (adherence) and other socio-demographic/socio-clinical factors
- To examine the cross-cultural validity of the SPUR model in a new patient population
- To explore the sensitivity, specificity, and adequacy of the SPUR model

4.2 Methods

4.2.1 Bespoke Validation Framework – Cross-cultural Validity

Chapter 3 sought to demonstrate the initial evidence of psychometric properties for the SPUR model in patients living with T2D. The VMATT2 study employed a bespoke validation framework informed by components of the COSMIN criteria, FDA PRO validation guidance, and validation protocols/studies of other PROMs of MA in T2D.[186,187,266,267,269,270] Chapter 4 used elements of this framework to develop a method with a more significant focus on hypothesis testing as well as construct and known-group validity using previously validated COPD specific health-outcome models that are described in detail below.

4.2.2 Pilot Study

4.2.2.1 Study Population & Sample Size

The pilot study was designed and delivered to examine face/content validity, acceptability, and interpretability of SPUR among a new sample population – individuals living with COPD. This pilot approach followed best practice implemented in the PPI approach discussed in Chapter 3, by actively involving patients in the review and design of the outcome measure.[186,187] A convenience and snowball sampling method was used to recruit patients, with a recruitment target range of 5-10 patients (~5-10% of final study population estimated – See Section 4.2.3.3).

In the previous pilot study, HCPs views were also explored. However, these HCPs included CPs and MO experts with no specialism in either T2D or respiratory disease. Hence, the sample size and previous responses on the SPUR model discussed in Chapter 3 were deemed sufficient from the perspective of HCPs.

4.2.2.2 Patient Recruitment

Local pharmacies in Richmond and Kingston were contacted to request participation in the pilot. Informed consent was requested from eligible patients using a bespoke consent form (Appendix R) prior to participation or data collection. Patients were also provided with a PIS (Appendix S).

Inclusion Criteria

1. Patients aged 18 years and over.
2. Patients diagnosed with COPD
3. Patients using at least one medicine for COPD including oral or inhaled forms for a minimum of 6 months.
4. Capable of understanding and willing to provide voluntary informed consent before taking part in the study.

Exclusion Criteria

1. Patients with an unconfirmed diagnosis of COPD
2. Patients diagnosed with COPD with less than 6 months of pharmacological treatment
3. Patients who are illiterate or unable to complete the questionnaire due to a language barrier.
4. Severe mental illness or disabilities that would preclude independent completion of the survey e.g., severe learning disability/severe dementia
5. Patients with extremely severe psychiatric illness or comorbidity e.g., cancer/HIV. Patients involved in a CTIMP at the time of the study

4.2.2.3 Data Collection

The pilot study used a mixed-method approach with the inclusion of a quantitative Likert scale survey in addition to participant demographics and qualitative feedback on the 45-item SPUR model.

4.2.2.4 Patient Questionnaire

The same questions used for the T2D pilot study were repurposed with the term ‘COPD’ throughout all relevant statements in the model. The items were both quantitative (n=5) and

qualitative (n=1) in nature (Appendix T). The demographic questions included in the patient questionnaire covered the following characteristics: age, ethnicity, gender, and highest level of education. Specifically, the pilot sought to investigate several components of the SPUR model design, including the acceptability of the questionnaire length, patients' ability to independently complete the questionnaire, and the relevance of the questions to their COPD diagnosis. Additionally, patients were encouraged to pinpoint specific questions or questionnaire sections they found inappropriate or difficult to answer. Similarly to the previous pilot study, this data collection phase aimed to provide initial face and content validity of the SPUR questionnaire in a new sample population, which would also inform early cross-cultural validity of the overall SPUR model in a new chronic condition.

4.2.2.5 Data Analysis

Data were collated and analysed in Microsoft Excel software. Descriptive statistics, such as the mean, were calculated for quantitative Likert scale responses. Given the small sample size, no further analyses, such as between-group differences based on socio-demographic characteristics, were conducted at this stage.

4.2.2.6 Ethical Approval

Ethical approval for the pilot study was provided by the KU REC on 19th December 2019. The ethical application title and allocated study number for this pilot project is: 1819 066.1 – ‘Validating an adherence measuring tool in patients living with COPD”. The pilot study began in Jan 2020 and was completed by March 2020.

4.2.3 Validation Study

4.2.3.1 Study Setting

This study, titled ‘Validating a Medication Adherence Tool in COPD (VMATC)’, was conducted as a single-arm, non-interventional, cross-sectional study among people living with COPD in England between January and December 2021. VMATC sought to provide early evidence of cross-cultural validity of the SPUR in a new chronic condition, while providing further evidence for psychometric properties of the model as a PROM of MA in people living with COPD.[352] The study was reported in accordance with the STROBE cross-sectional checklist.[279] The study was conducted at a secondary care site (Kingston Hospital NHS Foundation Trust) in Southwest London between January to December 2021

4.2.3.2 Study Population

The initial VMATC protocol was designed to reflect the original multi-arm protocol of VMATT2 and therefore intended to include both community and secondary care recruitment settings. Due to the timing of the study during the Covid-19 pandemic, it was agreed among the research team that opportunistic inclusion in the research study of those already admitted to hospital would be appropriate. However, actively recruiting participants in community settings presented a potential risk to pharmacy staff and patients in terms of unnecessary Covid-19 exposure. Based on risk *vs* benefit discussion, it was agreed to only proceed with the hospital arm of the VMATC study. The inclusion and exclusion criteria of the secondary care sample for this study are the same as those described in section 4.2.2.2.

4.2.3.3 Sample Size

The Covid-19 pandemic, intermittent lockdowns and research restrictions led to a reduction in the initial recruitment phase of the study from 6 to 4 months. Based on the Trust’s previous annual COPD admissions (n=230-368), an optimistic admission rate of 10 patients per week was projected, providing a total sample size of 160 patients over the 4-month period. The initial recruitment of 10 patients living with COPD on the Trust acute admissions unit

revealed that 30% (n=3) were too acutely unwell to participate in survey-based research and/or had an excluding factor. Therefore, approximately 25-30% (n=40-48) of the total predicted sample were expected to be ineligible due to acute illness, active cancer treatment, or significant co-morbidities such as dementia as defined in the exclusion criteria. A final representative minimum sample size of 92 participants based on the admission rate, with a 5% (MoE) and 95% CI, was generated using Raosoft[280] and rounded up to 100 for the final study sample.

4.2.3.4 Recruitment & Sampling Technique

In line with local GCP, the same recruitment and sampling strategy outlined in Chapter 3 for VMATT2 was repeated with the new VMATC sample. As a summary, homogenous purposive sampling strategy was used to encourage selection of the target group for recruitment *vs* random convenience sampling.[186,187,266–270] This method ensures that the sample is recruited in an efficient and timely manner, which was critical given the limited recruitment timeframe imposed by Covid-19 restrictions during the delivery of the study.

In line with the previous VMATT2 protocol, the direct clinical care team was responsible for identifying and approaching potentially eligible patients to discuss their enrolment on VMATC. Those that met the inclusion/exclusion criteria were identified in either in-patient wards or suitable outpatient clinics. The clinical care team notified the researcher of eligible patients who expressed interest in participating.

Following an expression of interest, the researcher approached patients to complete the consent process (Appendix U) and provide further information, including the PIS (Appendix V). The consent form also included a statement providing consent for the researcher to access the patient's individual electronic health record (EHR) and SCR, where available, to collect additional socio-clinical data relevant to the study e.g., comorbidities and pharmacy

medication records. Patients were then asked to complete the study questionnaire. Upon completion, a copy of the signed consent form and a written declaration of participation in the study was added to individual patient's notes.

4.2.3.5 Data Collection

4.2.3.5a Data Collection Tool

Study participants completed the questionnaire (Appendix W) that included the 45-item SPUR model with the term 'Type 2 Diabetes' replaced with 'COPD'. Notably, the early validation of the SPUR-27 model for T2D (VMATT2) was conducted during the recruitment for the VMATC study. VMATT2 presented evidence supporting the psychometric properties of the shorter SPUR-27 model that consists of 27 items. Therefore, while patients for VMATC completed the whole questionnaire, only the results obtained using the SPUR-27 tool were analysed to explore the cross-cultural validity and psychometric properties of the novel version of the PROM in this new sample population. Moreover, these studies were conducted in parallel, hence VMATT2 data analysis and the inception of SPUR-27 had not occurred prior to the ethics submission for VMATC. To assess symptom severity, the standardised model (CAT) was integrated into the study questionnaire. The Inhaler Adherence Score (IAS) was also included in the questionnaire to collect comparative self-reported MA data.[191] The IAS contains four Likert scale items scored from 1-5 that assess adherence to inhaler therapy with a total mean score of five indicating positive MA. The model has been validated in patients diagnosed with both asthma (α=0.086) and COPD (α=0.80), with acceptable psychometric properties reported for both cohorts.[353] Moreover, the PROM did not require license approval and was easy to collate within a data collection tool. Hence, with the psychometric properties and these factors in mind, the IAS was selected for use in the study. Items pertaining to socio-demographic data (age, gender, ethnicity, income,

marital status, and education) were collected in addition to information regarding patients' residential status and whether they received a package of care. Relevant socio-clinical data were also collected, such as smoking status, the number of prescribed medicines for respiratory disease (including inhaled therapy and oral medications), co-morbidities, COPD symptom severity, exacerbations, use of rescue packs, vaccination status (influenza & Covid-19), inhaler technique counselling, previous COPD education, and the number of GP visits. These data were obtained through patient self-reporting, or where available and with consent, from patient's medical record such as the SCR or EHR. To help classify and characterise patients' COPD diagnosis and symptom severity, data for disease-related measures, such as GOLD, the mMRC Dyspnoea scale, as well as lung function tests including FEV1 and FVC, were collected when available through medical records. All retrospective data reported within the previous 12 months prior to study participation were considered eligible for inclusion.

4.2.3.5b Data Collection Methods

A paper copy of the questionnaire was provided to each participant after completing the consent procedure. Where possible, participants were given as much time as reasonable to complete the questionnaire by themselves. For example, the author would attend the hospital ward in the morning to identify new patients with the clinical care team. Patients would then be left to review the study materials for a few hours before the author returned to the ward to either proceed with study procedures or confirm that the patient did not wish to participate. Upon completion, questionnaires were assessed to ensure all answers had been provided. If items were missed, participants were informed and provided with the opportunity to fill in the items as well as given information by the authors on why missing items should be addressed to improve the results of the study. The same procedures for improving accessibility for some participants, as outlined in section 3.4.1.2e, were applied to the VMATC study.

4.2.3.6 Data Analysis

4.2.3.6a Factor Analyses

As discussed in Chapter 3, EFA is a data-driven technique that can be useful in the early development of PROMs to assess underlying structures within the model.[299] Comparatively, CFA is useful in the determination of validity for pre-specified models whereby there are clear relationships between observed variables and underlying factors.[300] However, in the absence of strong *a posteriori* evidence to provide predictions on both the number of factors and expected loadings within a correlation matrix, CFA may be less appropriate.[354,355] When evaluating measurement properties of PROMs in cross-cultural validity analyses, Multi-Group Confirmatory Factor Analysis (MGCFA) is recommended.[186] The SPUR-27 model has only demonstrated psychometric properties in one sample population of individuals living with T2D. In these instances, Gignac[355] recommends the implementation of Partial CFA (PCFA) to provide further evidence of a model's plausibility without the use of CFA techniques such as Structural Equation Modelling (SEM). Moreover, PCFA in addition to EFA can provide information to support decisions on whether future CFA is appropriate.[355]

To this extent, both EFA and PCFA were employed in this study – recommendations on suitable implementation and evaluation of outcomes from these analyses were sought from the COSMIN criteria and other suitable validation studies that employed both methods, which are described in more detail below.[186] To determine the eligibility of the data for further analysis, the KMO measure of sampling adequacy and Bartlett's test of sphericity were used. Eigenvalues >1 and visual inspection of a matching inflection points on a scree plot were used to identify initial factors. A Direct Oblimin rotation was used for EFA, with factor loadings >0.32 being considered valid.[287] For PCFA, Gignac's[355] suggested methodology was followed including the use of Maximum Likelihood Analysis (MLA), NFI,

CFI, TFI, and RMSEA. MLA provides an implied model Chi-square (χ^2) value that can be used in tandem with the null model Chi-square value provided through Barlett's test of sphericity to calculate the relevant fit indices. Fit indices are reflective of the discrepancy between the empirical model (implied Chi-square) and predicted model (null Chi-square) and can be used to support decisions on whether to accept or reject a model – in essence, PCFA is a useful approach to provide evidence of factorial validity for EFA derived models.[355,356] A value of ≥0.9 was expected for NFI, CFI, and TLI, and a value of <0.08 was expected for RMSEA.[186,357,358]

4.2.3.6b Reliability Analyses

The internal consistency of the SPUR-27 model and its individual factors was assessed using Cronbach's alpha (α), with a value of α ≥0.8 indicating strong evidence of reliability.[359] ITCs and ICCs were also computed, with a value greater than 0.3 and 0.5 being deemed acceptably for each, respecitvely.[360]

Test-retest reliability procedures were documented as part of the initial protocol for VMATC. This study was subject to ethical consideration during the delivery of VMATT2 when a decision was made based on the Covid-19 pandemic to discontinue test-retest reliability procedures as outlined in Chapter 3. At the time ethics approval was granted for VMATC, partial Covid-19 lockdown measures were still in place, hence it was also agreed that test-retest reliability procedures would not be pursued as part of this current study during that time.

4.2.3.6c Construct, Convergent & Concurrent Validity

While VMATT2 provided early evidence of the multidimensional psychometric properties of SPUR and the overall factorial structure, a key objective of VMATC was to determine cross-

cultural validity of this model in a new sample population of individuals living with COPD. To this extent, VMATC focused on exploring convergent validity of the overall SPUR-27 model with the IAS. [48] To assess concurrent validity, the SPUR-27 scores were compared to MPR. MPR was calculated using the SCR or EHR, and an MPR value of ≥80% was used as the cut-off to determine participant adherence in line with the procedures used in the previous VMATT2 study.[291] Evidence of construct validity, interpreted as the overall underlying construct of MA or non-adherence, was inferred from data to support hypothesis on correlations for both the convergent and concurrent validity of SPUR against the two previously validated comparators. More specifically, it was expected that SPUR-27 would be significantly and positively correlated with scores for IAS and MPR.[361]

4.2.3.6d Known-Group Validity

Similarly, hypothesis testing for construct validity can be supported with the robust demonstration of known-group validity.[186] Socio-clinical data were collected to explore several expected relationships between these variables and SPUR-27. In line with previously reported relationships, age and income were predicted to be positively associated with SPUR model, indicating greater adherence in older and affluent participants.[362] Conversely, an inverse relationship was expected with an increased comorbidity burden, higher numbers of prescribed respiratory medicines, COPD exacerbations, rescue pack use and GP visits within the previous 12-months.[362–366] These relationships were assessed using Spearman's Rank Correlation coefficients (ρ).

In addition, a Chi-Square analysis (χ^2) was conducted to evaluate the dynamic between adherence scores and the severity of COPD symptoms experienced by patients, assessed using the CAT score. Using the previous SPUR cut-off score of ≥80% to indicate adherence, patient groups were stratified using the CAT scores, with scores of 0-19 classified as low-

medium and scores ≥20 classified as high-very high in relation to symptom severity.[278] It was expected that individuals with less severe self-reported symptoms would report higher SPUR-27 scores, indicating higher MA. Other clinical outcomes associated with less severe COPD (lower GOLD classification, lower mMRC score, and better lung function results) were also expected to be associated with higher SPUR-27 scores.

Shapiro-Wilk tests were used to determine the normality of data. Consistently, non-normal distribution was identified ($p<0.05$), most likely due to a smaller sample size, hence non-parametric analyses such as Kruskal Wallis H tests were used to examine between group differences for SPUR-27 scores and socio-demographic data that were collected as either ordinal or categorical variables with >2 groups e.g., age, education. Wilcoxon signed-rank tests were conducted for variables with binary group coding e.g., vaccination status (yes or no within the previous 12-months).

4.2.3.6e Cut-off Determination & Adequacy Testing

As stated in sections *b* and *c* above, VMATC used a single comparative PROM (IAS) to support analyses for convergent validity and provide additional evidence of construct validity with a sequence of hypothesis testing. To build upon evidence provided in the hypothesis testing, VMATC also sought to explore novel score cut-offs for the SPUR model that could improve the model's capacity to discriminate between groups of patients based on socio-clinical factors such as symptom severity. The VMATT2 study focused on evaluating the multidimensional aspect of SPUR and therefore did not undertake cut-off determination testing. Furthermore, cut-off analyses are neither described in the COSMIN criteria nor FDA PRO validation guidance. Fawcett's[367] recommendations on methods for cut-off determination were implemented. A Receiver-Operator Characteristic (ROC) curve was generated in addition to Area Under the Curve (AUC) calculations to perform an ROC-AUC

analysis that could determine any new potential cut-off value that would provide the highest-sensitivity and specificity defined as:[368]

- Sensitivity - the ability of a measure to correctly identify patients with the outcome of interest e.g., adherence >80%.
- Specificity – the ability of a measure to correctly identify patients without the outcome of interest e.g., adherence <80%.

MPR has been demonstrated as a potentially unrealiable measure and may over-estimate MA, particularly in the context of data collected during the Covid-19 pandemic.[278] Therefore, the IAS was chosen as the reference for the ROC-AUC analysis, whereby the ratio of positive:negative cases of patients achieving adherence using the IAS scoring methodology would provide the control sample for comparison. MPR was also included in the ROC-AUC analysis as a non-reference comparator to SPUR-27. Sensitivity and specificity data were generated for each model included in the ROC-AUC analysis as well positive and negative predictive values to provide an indication of model adequacy. Model adequacy can be defined as the congruence between the observed and predicted model.

Data were analysed using IBM SPSS Software Version 26.0 for Windows. Continuous data are expressed as a mean (x) and SD. Categorical data are reported as sample number (n) and percentage (%).

4.2.3.7 Ethical Approval

The VMATC protocol and study documentation were submitted via IRAS (ID:285590) for review with approval received from the NHS HRA REC (20/NW/0485) in January 2021.

4.3 Results

4.3.1 Pilot Study

A total of 21 patients diagnosed with COPD were invited to take part in the pilot study. After invitation, eight agreed to participate providing a response rate of 38.1%. Socio-demographic information was collected and are presented in Table 4.1. The modal age was equally split between 60-69 (n=4) and 70-79 (n=4) years-old participants. The sample were predominantly educated to GSCE level or equivalent and identified as white (n=7). Females represented just over one-third of the sample (n=3, 37.5%).

Table 4.1 – Patient Pilot Study Sample Characteristics

Parameter (n=8)	**Number (n,%)**	**Mode**
Age		60-69, 70-79
<60	0	
60-69	4, 50.0%	
70-79	4, 50.0%	
Gender		Male
Male	5, 62.5%	
Female	3, 37.5%	
Ethnicity		White
White	7, 87.5%	
Mixed/Multiple Ethnic Groups	0	
Asian/Asian British	0	
Black/African /Caribbean/ Black British	1, 12.5%	
Other	0	
Education		GCSE or Equivalent
No formal education	1, 12.5%	
GCSE or Equivalent	4, 50.0%	
A-Level or Equivalent	3, 37.5%	
Bachelors Degree or Equivalent	0	
Post-graduate Degree or Equivalent	0	

The quantitative results of the pilot survey, which included the same Likert-scale items (n=5) previously implemented in the pilot study described in Chapter 3, are described in Table 4.2. Respondents found the questions easy to answer and reported more positive results in terms of happiness to complete the questionnaire independently and beliefs about the impact of SPUR on their medicines when compared to the previous pilot. Similarly, the results

indicated in tandem with the previous pilot that the length of questionnaire was the item with the least positive response with a mean of 3.1, indicating some ambivalence among the pilot sample. Encouragingly, participants found the questions relevant to their COPD and no specific items were identified as difficult or a problem to complete. Finally, all eight participants completed 100.0% of the 45-item SPUR tool, indicating early evidence of perceived acceptability of the model as well as face and content validity that can be derived from the overall responses described in Table 4.2.

Table 4.2 – Pilot SPUR Feedback Results

Statement	Mean Score (n=8)
The questions were easy to answer	4.5
I am happy with the length of the questionnaire	3.1
I would be happy to complete the questionnaire by myself	3.8
I believe this questionnaire could help improve my relationships with medicines	3.8
The questions are relevant to my condition	4.3

4.3.2 VMATC Study

4.3.2.1 Study Sample Characteristics

Out of the 123 patients approached, a total of 100 participated in this study, resulting in a response rate of 81.3%. A breakdown of the recruitment flow is documented in Figure 4.1. Socio-demographic variables, including age, education, and income were collected (Table 4.3). The most common age range was 70-79 years, representing 41% of the sample (n=41) – unsurprisingly 76% were therefore retired. Most participants were white (90.0%) and had attained GCSE level education or equivalent (51.0%). The sample was fairly split in terms of gender, with just over half of participants identifying as female (52.0%). The vast majority (95.0%) lived either by themselves or with a family member, while roughly three-quarters of participants were not receiving social care at the time of recruitment (74.0%). The modal

range of the sample may also have been indicative of the modal marriage status, with 29% of the cohort reporting that they were widowed at the time of recruitment.

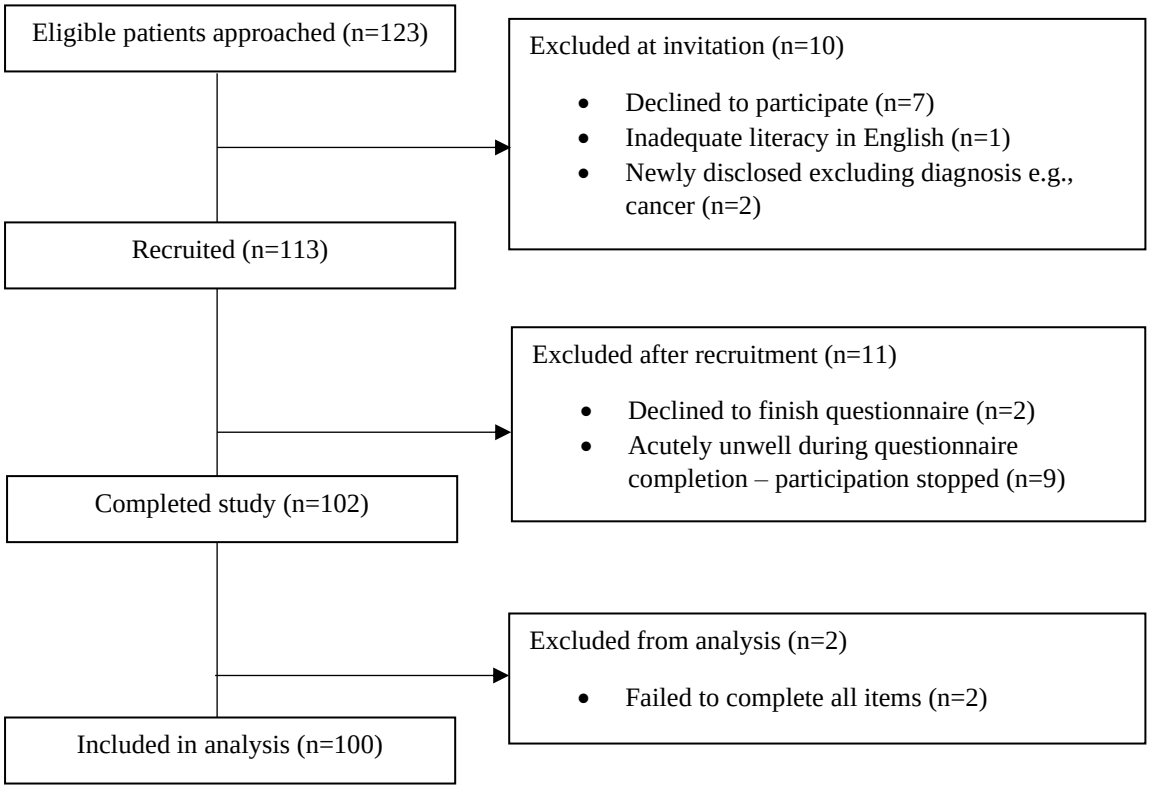


Figure 4.1 - Flowchart of Study Participant Sampling Procedure

Table 4.3 - Study Sample Characteristics

Parameter (n=100)	Number (n,%)	Mode
Age		70-79
18-29	0	
30-39	0	
40-49	2, 2.0%	
50-59	8, 8.0%	
60-69	14, 14.0%	
70-79	41, 41.0%	
80+	35, 35.0%	
Gender		Female
Male	48, 48.0%	
Female	52, 52.0%	
Other	0	
Ethnicity		White
White	90, 90.0%	
Black	3, 3.0%	
Asian	2, 2.0%	
Mixed	2, 2.0%	
Other	3, 3.0%	
Income		Retired
<£14999	3, 3.0%	
£15000-£24999	3, 3.0%	
£25000-£34999	3, 3.0%	
£35000-£44999	3, 3.0%	
£45000-£54999	0	
£55000-£64999	0	
£65000-£74999	1, 1.0%	
>£75000	1, 1.0%	
Unemployed	10, 10.0%	
Retired	76, 76.0%	
Education		GSCE or equivalent
No formal education	15, 15.0%	
GCSE or equivalent	51, 51.0%	
A-Level or equivalent	22, 22.0%	
Bachelors degree or equivalent	8, 8.0%	
Post-grad degree or equivalent	4, 4.0%	
Residential Status		Lives alone
Lives alone	48, 48.0%	
Lives with a family member	47, 47.0%	
Residential home	2, 2.0%	
Nursing home	3, 3.0%	
Receiving a package of care[a]		No package of care
No package of care	74, 74.0%	
Daily	5, 5.0%	
Twice a day	5, 5.0%	
Three times a day	3, 3.0%	
Four times a day	5, 5.0%	
24-hour care	8, 8.0%	
Marital Status		Widowed
Single	24, 24.0%	
Married	26, 26.0%	
Divorced/Separated	19, 19.0%	
Widowed	29, 29.0%	
Civil Partnership	2, 2.0%	

Notes:[a]A package of care may include social care support activities e.g. personal care or support with daily activities such as cooking or leaving the house

Of the study sample, 67.0% reported being ex-smokers, with an average pack year history of 39.33 ± 26.03 among both smoking and ex-smoking participants (Table 4.4). BMI data were available for all participants, with a mean BMI of 27.38 ± 6.88 kg/m2, indicating that the cohort skewed towards being overweight in accordance with BMI classification (BMI ≥25). A high comorbidity burden was observed across the sample, with participants being diagnosed with a mean of 7.69 ± 3.59 comorbidities at the time of recruitment. Furthermore, despite recruitment taking place during the Covid-19 pandemic when primary care access was limited, a significant range of COPD exacerbations, rescue pack use, and GP visits were reported within the previous 12-month period. Influenza vaccine uptake (n=54) within the cohort was comparable to data previously reported for uptake among people diagnosed with a chronic condition in England (50.4%). Encouragingly, the entire cohort had received a Covid-19 vaccination. Inhaler technique counselling was more common than counselling related to COPD as a diagnosis itself (64.0% *vs* 26.0%).

Table 4.4 – Study Sample Socio-clinical Characteristics

Parameter (n=100)	Number (n,%)	Mean ± SD	Range	Mode
Smoking Status				Ex-smoker
Smoker	22, 22.0%			
Ex-smoker	67, 67.0%			
Never smoked	11, 11.0%			
Pack Years[a]	89, 89.0%	39.3 ± 26.03	1-150	30
Clinical Factors				
BMI (kg/m^2)		27.34 ± 6.88	12.5-46.7	23.97
Number of COPD medicines[b]		2.69 ± 1.16	1-5	2
Number of conditions		7.69 ± 3.59	2-18	9
Number of COPD exacerbations		1.93 ± 2.80	0-20	0
Number of rescue packs		1.28 ± 2.22	0-12	0
Number of GP visits		2.24 ± 3.49	0-12	1
Influenza Vaccine				Vaccinated
Vaccinated	54, 54.0%			
Not Vaccinated	46, 46.0%			
Covid-19				Vaccinated
Vaccinated	100, 100.0%			
Inhaler Technique Counselling				Yes
Yes	64, 64.0%			
No	36, 36.0%			
Counselling on COPD Diagnosis				No
Yes	26, 26.0%			
No	74, 74.0%			

Notes:[a]One pack year equals one year of smoking 20 cigarettes, or equivalent, per day [b]Includes any prescribed medicine for COPD e.g. inhaled therapies or oral dosage forms

Abbrevations: GP, general practice

4.3.2.2 Factor Analyses

Pre-requisite testing identified a KMO measure of sampling adequacy >0.7 along with a significant Bartlett's test of sphericity ($\chi 2 = 1489.802$, $p < 0.001$). The initial EFA resulted in an 8-factor solution (eigenvalues >1) that explained 62.2% of the variance. However, one item (Item 29) had an inadequate factor loading of <0.32 in the rotated model and was removed. Post-removal, the 8-factor solution demonstrated only one item (Item 33) loaded on to factor 8. Removing Item 33 led to a 7-factor rotated solution with only 2 items loading on Factors 5 and 6, respectively. To explore the congruence of the 7-factor solution identified in VMATT2, EFA was repeated while fixing the number of factors at seven. The new 7-factor solution (eigenvalues >1) explained greater model variance (68.9%) than the previous 8-factor model (Table 4.5). Furthermore, all 27 items observed loadings >0.32. It was identified

that Factor 7 contained only two items, however the average loading was moderately high (0.666) and therefore this solution was retained for further analysis (Table 4.6).[287]

Table 4.5 – Fixed 7-factor Solution Eigenvalues

Factor	Eigenvalue	Variance (%)	Cumulative Variance (%)
1	7.834	29.015	29.015
2	2.998	11.103	40.118
3	1.951	7.228	47.346
4	1.633	6.049	53.395
5	1.486	5.503	58.898
6	1.447	5.359	64.257
7	1.250	4.631	68.888

Table 4.6 - SPUR-27 Item Content & Factor Loadings

Item	Factor	Subscale	Factor Loading	Average Factor Loading
Medications for my COPD don't do anything for me[a]	1	Treatment Consequence	0.889	0.676
There is no point in taking medications for my COPD[a]	1	Treatment Consequence	0.849	
My treatment helps my COPD	1	Treatment Consequence	0.834	
My COPD is likely to get worse if I don't follow my treatment plan	1	Treatment Consequence	0.612	
I believe I can stop my treatment for my COPD when I feel better[a]	1	Treatment Consequence	0.611	
Sometimes I don't follow my treatment plan exactly[a]	1	Treatment Consequence	0.481	
I will have to take a treatment for my COPD for the rest of my life	1	Treatment Consequence	0.459	
My COPD affects my social life[a]	2	Interpersonal Relationships	0.817	0.610
My COPD affects my relationships with those I care about[a]	2	Interpersonal Relationships	0.754	
I find it easy to manage the different medications I take	2	Interpersonal Relationships	0.438	
My COPD should be taken seriously.	2	Interpersonal Relationships	0.429	
I am able to follow my treatment plan.	3	Adherence Behaviour	0.844	0.677
I'm the kind of person who will follow their treatment plan exactly.	3	Adherence Behaviour	0.817	
I find it easy to follow my treatment plan when I am not at home.	3	Adherence Behaviour	0.636	
Following my COPD treatment plan lets me do the things I want to do.	3	Adherence Behaviour	0.411	
Precisely following doctors' recommendations is the best way for me to stay healthy.	4	Treatment Motivation	0.928	0.758
If my doctor recommends that I do something, I do it.	4	Treatment Motivation	0.875	
I trust the doctors' recommendations.	4	Treatment Motivation	0.845	
It is essential that I follow my treatment plan.	4	Treatment Motivation	0.384	
My treatment affects my sex life[a]	5	Treatment Control	0.789	0.665
I find it easy to get my treatment for my COPD.	5	Treatment Control	0.723	
I have found ways to deal with my COPD.	5	Treatment Control	0.484	
I am satisfied with the level of information I have about my COPD.	6	Knowledge Satisfaction	0.836	0.722
I am satisfied with the level of information I have about my treatment.	6	Knowledge Satisfaction	0.795	
I completely understand my COPD.	6	Knowledge Satisfaction	0.536	
I find it easy to take my medications for my COPD.	7	Ease of Use & Access	0.725	0.666
Fighting for my health is my highest priority.	7	Ease of Use & Access	0.606	

Notes:[a]Reverse coded item

Additionally, PCFA using MLA was performed on the 7-factor model with a repeated Direct Oblimin rotation. The implied model $\chi 2$ value was reported at 280.956, df=183. The NFI (0.96), TFI (0.97) and CFI (0.93) were >0.9, and the RMSEA was <0.08 (0.059). These results provided strong early evidence of model fit through PCFA.

It is worth noting that the item-to-factor mapping in the SPUR-27 model for this population differed from that observed in the previous VMATT2 study. For example, item 6 – 'Sometimes I don't follow my treatment plan exactly', currently mapped to Factor 1 (Treatment Consequence), was previously designated under the Usage domain and under Factor 5 (Adherence Behaviour) in the former study. When comparing the different models for each population, item-to-factor loading continuity occurred for 19 out of 27 items (70.4%) identified in the structure using EFA (Table 4.7). This finding may suggest incongruence between the models, populations, or potentially limitations around the approach to factorial analysis that this Chapter will address in the discussion.

Table 4.7 – Item-Factor/Subscale Loading for VMATT2 *vs* VMATC

Item	VMATT2 Factor/Subscale	VMATC Factor/Subscale
Precisely following doctors' recommendations is the best way for me to stay healthy.	Treatment Motivation	Treatment Motivation
I trust the doctors' recommendations.	Treatment Motivation	Treatment Motivation
If my doctor recommends that I do something, I do it.	Treatment Motivation	Treatment Motivation
It is essential that I follow my treatment plan.	Treatment Motivation	Treatment Motivation
Fighting for my health is my highest priority.	Treatment Motivation	Ease of Use & Access
My X[a] affects my social life.[b]	Interpersonal Relationships	Interpersonal Relationships
My X affects my relationships with those I care about.[b]	Interpersonal Relationships	Interpersonal Relationships
My treatment affects my sex life.[b]	Interpersonal Relationships	Treatment Control
There is no point in taking medications for my X.[b]	Treatment Consequence	Treatment Consequence
Medications for my X don't do anything for me.[b]	Treatment Consequence	Treatment Consequence
I believe I can stop my treatment for my X when I feel better.[b]	Treatment Consequence	Treatment Consequence
My X should be taken seriously.	Treatment Consequence	Interpersonal Relationships
I will have to take a treatment for my X for the rest of my life.	Treatment Consequence	Treatment Consequence
My treatment helps my X.	Treatment Consequence	Treatment Consequence
My X is likely to get worse if I don't follow my treatment plan.	Treatment Consequence	Treatment Consequence
I am satisfied with the level of information I have about my X.	Knowledge Satisfaction	Knowledge Satisfaction
I completely understand my X.	Knowledge Satisfaction	Knowledge Satisfaction
I am satisfied with the level of information I have about my treatment.	Knowledge Satisfaction	Knowledge Satisfaction
Sometimes I don't follow my treatment plan exactly.[b]	Adherence Behaviour	Treatment Consequence
I'm the kind of person who will follow their treatment plan exactly.	Adherence Behaviour	Adherence Behaviour
I am able to follow my treatment plan.	Adherence Behaviour	Adherence Behaviour
I have found ways to deal with my X.	Treatment Control	Treatment Control
Following my X treatment plan lets me do the things I want to do.	Treatment Control	Adherence Behaviour
I find it easy to take my medications for my X.	Ease of Use & Access	Ease of Use & Access
I find it easy to manage the different medications I take.	Ease of Use & Access	Interpersonal Relationships
I find it easy to get my treatment for my X.	Ease of Use & Access	Treatment Control
I find it easy to follow my treatment plan when I am not at home.	Ease of Use & Access	Adherence Behaviour

Notes:[a]X denotes either ‘COPD’ or ‘diabetes’ for VMATC and VMATT2 SPUR models, respectively;[b]Reverse coded item

4.3.2.3 Score Distribution & Reliability

As previously stated, the SPUR-27 model implemented Likert scale items with scores from 1-5. Higher scores were interpreted as positively indicative of MA. Individual item scores demonstrated a predominantly left-skewed distribution (3.44-4.74) and mean total score 4.19 ± 1.09 across the entire 27-item model. The mean SPUR-27 score was 83.82 ± 11.53 (Table 4.8). Similarly to VMATT2, several of the individual factors and their relevant subscale scores observed some floor and ceiling effects, however this did not translate into the overall SPUR-27 model (Range 44.44-99.26)

Table 4.8 - SPUR-27/Subscale Score

Overall Model/Subscale	Mean Score (% ± SD)	Range (%)	
		Min	Max
SPUR-27	83.82 ± 11.53	44.44	99.26
F1 – Treatment Consequence	86.96 ± 14.28	40.00	100.00
F2 – Interpersonal Relationships	77.26 ± 23.50	20.00	100.00
F3 – Adherence Behaviour	88.69 ± 13.98	37.14	100.00
F4 – Treatment Motivation	82.07 ± 19.20	20.00	100.00
F5 - Treatment Control	80.93 ± 17.06	20.00	100.00
F6 – Knowledge Satisfaction	74.10 ± 22.66	20.00	100.00
F7 – Ease of Use & Access	84.65 ± 15.48	35.00	100.00

In addition to average factor loadings and mean scores for each factor, it is also recommended that internal estimates of consistency (α) are reported for each factor as well as the overall model.[186] Typically, these values would be reported after iterative reduction of the model using a combination of methods such as EFA and removal of items that can improve the overall α for the model as demonstrated in Chapter 3. However, the reliability analysis did not identify any items that if removed would have resulted in an increased α. Hence, internal

consistency estimates were directly interpreted for the 27-item model produced using the fixed 7-factor EFA described in Table 4.6. The overall internal consistency estimates to factors 1-7 ranged from moderate to very strong (0.504-0.850) (Table 4.9).[359] Furthermore, the overall α value for the entire SPUR-27 model was strong (0.893). The ITC values varied between 0.263 and 0.652. The ICC values were considered acceptable (>0.5) with a value of 0.893 (95% CI: 0.860-0.921).[360] The inter-factor correlations were mainly significant (p<0.05 or p<0.01) and ranged from -0.008 to 0.535. Notably, the overall SPUR-27 α was marginally and insignificantly smaller than that reported from SPUR-27 in the VMATT2 study (0.893 *vs* 0.900 – See Section 3.5.1.2b)

Table 4.9 - Inter-factor Correlations & Internal Consistency (IC) Estimates

	Inter-Factor Correlations							IC
Factors	F1	F2	F3	F4	F5	F6	F7	α
F1 Treatment Consequence (R)[a]	1	-0.008	.417[b]	.278[b]	.389[b]	.216[c]	0.128	0.850
F2 Interpersonal Relationships (S)		1	0.177	.336[b]	.234[c]	.528[b]	.535[b]	0.666
F3 Adherence Behaviour (U)			1	.524[b]	.522[b]	.528[b]	.329[b]	0.707
F4 Treatment Motivation (P)				1	.529[b]	.491[b]	.460[b]	0.829
F5 Treatment Control (R)					1	.418[b]	.360[b]	0.682
F6 Knowledge Satisfaction (R)						1	.459[b]	0.753
F7 Ease of Use & Access (U)							1	0.504

Notes: Notes:[a]Letters associated with each factor indicate the original SPUR domain (Social, Psychological, Usage, and Rational);[b]p<0.01;[c]p<0.05

4.3.2.4 Construct, Convergent & Concurrent Validity

The study examined the convergent and concurrent validity of the SPUR-27 model by comparing it with the IAS total score and MPR, respectively. The results showed strong significant positive correlations (ρ=0.645, p<0.001) between the SPUR-27 model and the IAS total score, providing evidence of convergent validity. Furthermore, a weaker but significant positive correlation (ρ=0.295, p<0.01) was found between the SPUR-27 model and MPR, providing evidence of concurrent validity. It is important to note that construct validity refers

to the degree to which a test or measurement tool measures what it claims to measure. These initial findings therefore also support the overall construct validity of the model by demonstrating the results of expected relationships stated as part of a priori hypothesis development e.g., Higher IAS and MPR scores are indicative of MA, hence significant positive correlations with the SPUR-27 model were expected.

4.3.2.5 Known-Group Validity

Known-group analyses also inform a critical element of overall construct validity. Several predicted relationships between SPUR-27 and socio-clinical factors were reported in the methods prior to the analyses. SPUR-27 demonstrated a significant weak positive correlation with patient income (ρ=0.269, p<0.01), suggesting that more affluent participants had a greater likelihood of adhering to their treatment. In contrast, a significant weak negative correlation was observed between the SPUR-27 score and the number of COPD exacerbations reported in the 12 months prior to the study (ρ=-0.201, p<0.01), hence one might conclude that poorer MA was associated with a higher risk of an exacerbation of COPD symptoms. Both findings are congruent with earlier predictions and therefore provide strong early evidence of known-group validity, as well as supporting the overall construct validity of the model. Furthermore, the SPUR-27 score was found to have a positive correlation with age, and a negative correlation with the number of respiratory medicines, comorbidities, GP visits, and rescue packs used in the previous 12 months. While these group relationships reported correlations that were congruent with expected effect directions, they were not statistically significant (p>0.05).

No significant differences (p>0.05) in SPUR-27 score were observed between groups (Kruskal Wallis H or Wilcoxon Signed Rank Test) based on socio-demographic/clinical characteristics such as age, ethnicity, gender, income, marital status, residential status, levels

of social care support, vaccination status, COPD/inhaler related education, GP visits, exacerbations, or rescue pack use.

The CAT score was implemented to discern patient groups based on COPD symptom severity. Cross-tabulation of SPUR-27 scores and COPD symptom severity (low-medium *vs* high-very high) demonstrated a significant association ($p<0.01$, Chi-Square ($\chi 2 = 8.570$)). Figure 4.2 demonstrates the distribution of adherent and non-adherent patients (defined using an ≥80% SPUR-27 cut-off) against CAT score responses. Hence, SPUR-27 could reliably distinguish patients based on symptom severity and known-group validity was established for this cohort based on this classification.

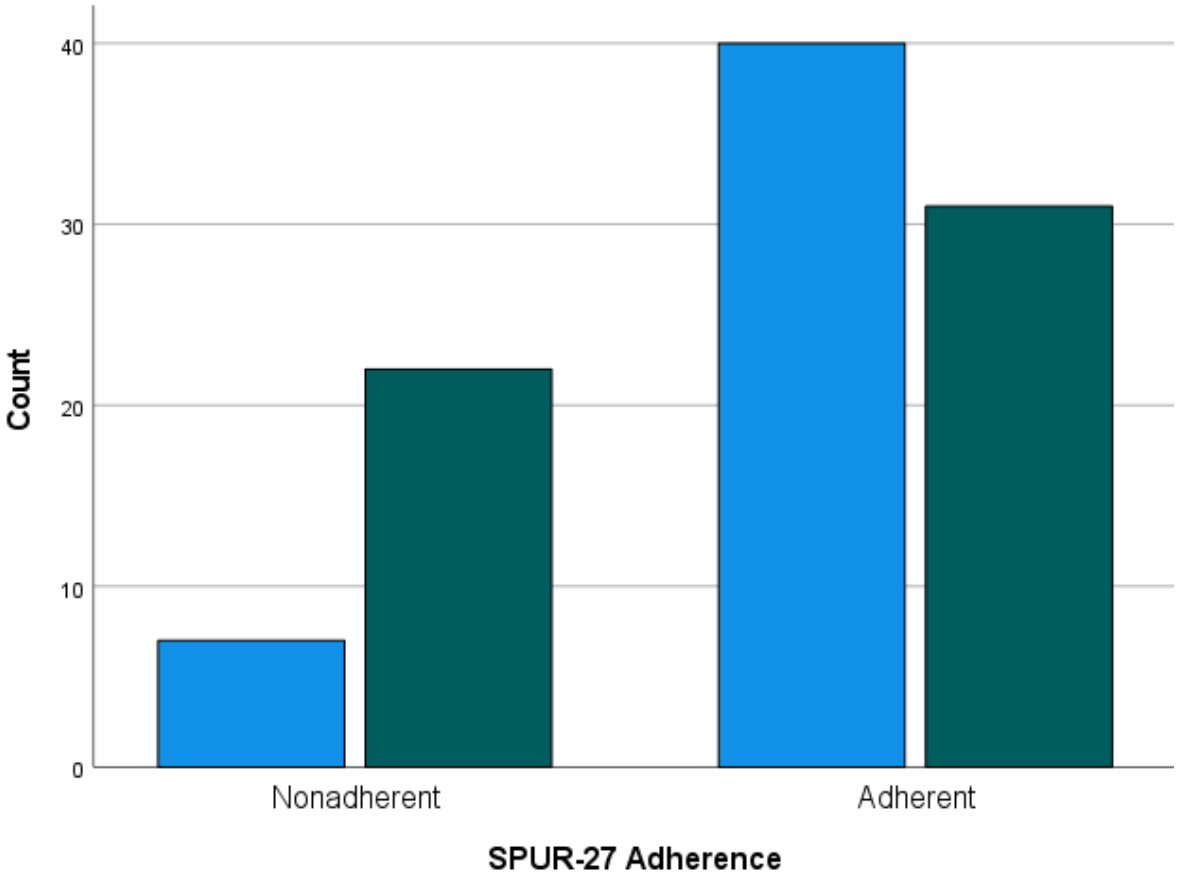


Figure 4.2 - SPUR-27 Distribution of Adherent and Non-Adherent Patients by CAT Score.

Notes: Light blue columns = Patients reporting a low-medium CAT score; Dark Green columns = Patients reporting a high-very high CAT score (scores of 0-19 are classified as low-medium and scores ≥20 classified as high-very high).

Unfortunately, less than 5% (n=4/100) of the study sample had available results for GOLD COPD classification, MRC Dyspnoea scale scores, or lung function tests (FEV1/FVC). Therefore, these results were not included in the known-group validity analyses.

4.3.2.6 Cut-off Determination

The previous VMATT2 study, among others, have shown that MPR may be an unreliable measure of MA. Therefore, the decision was made to use the IAS as the reference standard in this analysis to develop a ROC-AUC analysis that incorporates both SPUR-27, as well as MPR as an additional reference (Figure 4.3). The adherence rate, as assessed by IAS, was

found to be poor, with a positive to negative case ratio of 36:64, where positive cases were defined as patients who were adherent based on the IAS scoring methodology. In contrast, using a cut-off score of >80, ratios of 42:58 and 72:28 were reported for SPUR-27 and MPR respectively.

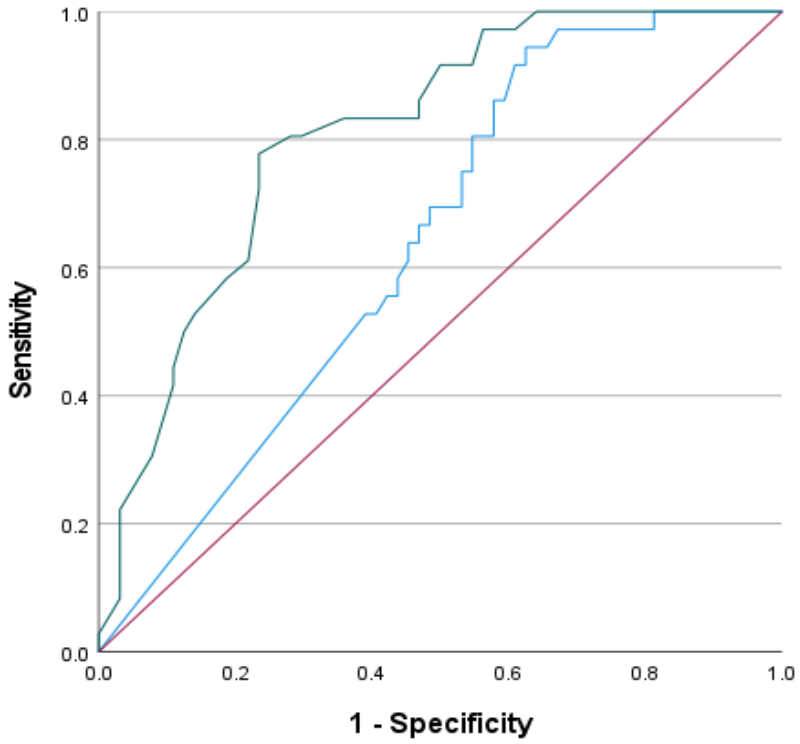


Figure 4.3 – ROC Curve

Notes: Sources for ROC; red line = reference line; blue line = MPR; green line = SPUR-27. The ROC is indicative of the AUC with results closer to 1 (100%, top left corner) indicating a greater ability to distinguish between groups.

The SPUR-27 model observed an ROC-AUC >80%, while MPR produced an ROC-AUC of 63.8% (95% CI; 0.531, 0.745) (Table 4.10). Based on the ROC-AUC coordinates, a new cut-off value of 87% to determine adherence *vs* non-adherence was established for the SPUR-27 model. This cut-off value provided a sensitivity of 0.806 and an inverse specificity of 0.281, with 37.0% of the cohort identified as adherent.

Table 4.10 – ROC-AUC Analysis

Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
MPR	.638	.055	.022[a]	.531	.745
SPUR-27	.809	.043	.000[b]	.725	.893

Notes: [a]$p<0.05$; [b]$p<0.01$

Sensitivity and specificity data were used to inform the new SPUR-27 cut-off score, however additional analyses were conducted to explore the impact of the cut-off on previously confirmed metrics of validity, such as known-group validity. A Chi-Square analysis was repeated that compared the CAT and SPUR-27 (87 cut-off). The analysis demonstrated a significant difference between the known groups defined by the new cut-off score ($\chi 2=8.903$, $p=0.003$). Hence, known-group validity could be established for SPUR-27 using the new cut-off score (Figure 4.4)

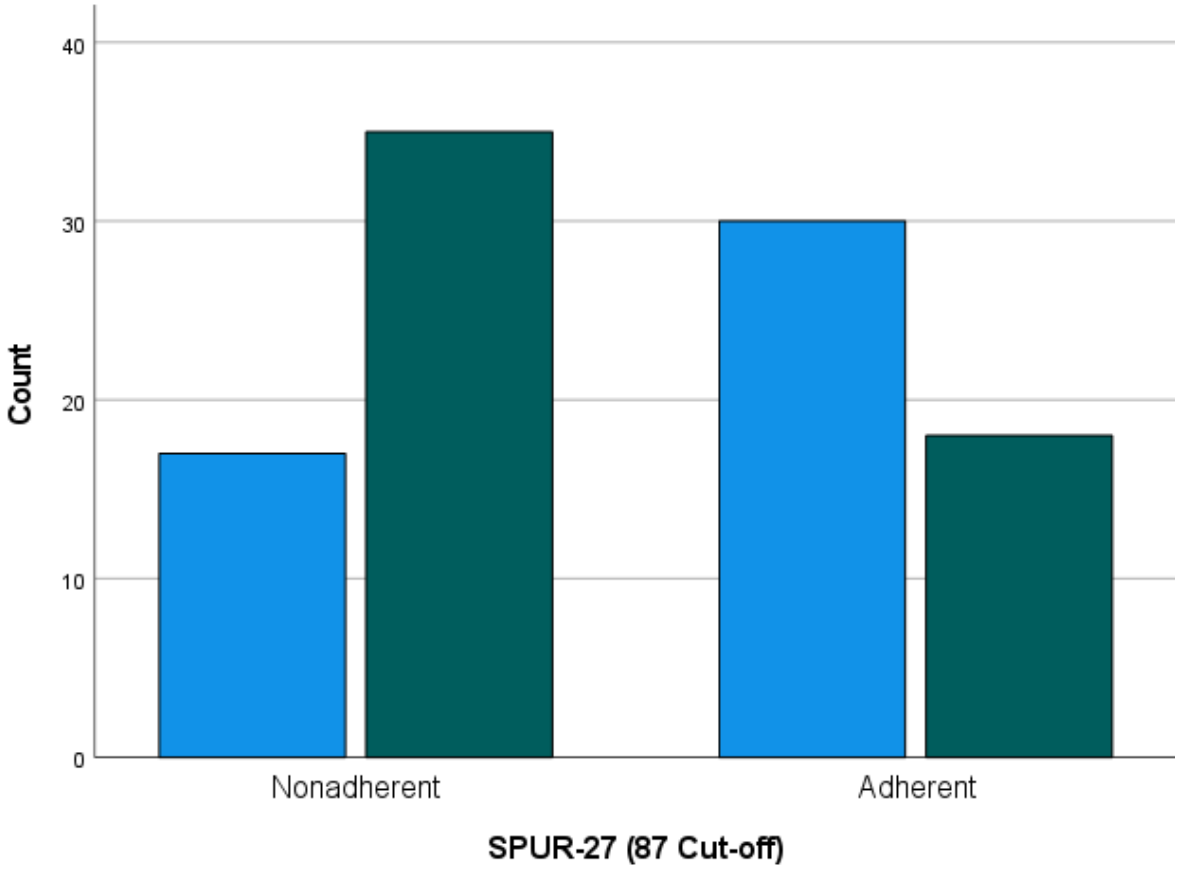


Figure 4.4 - SPUR-27 Distribution (87-point cut-off) of Adherent and Non-Adherent Patients by CAT Score.

Notes: Light blue columns = Patients reporting a low-medium CAT score; Dark Green columns = Patients reporting a high-very high CAT score (scores of 0-19 are classified as low-medium and scores ≥20 classified as high-very high).

4.3.2.7 Model Adequacy

Goodness-of-fit tests and sensitivity analysis can help to form the statistical basis for determining overall model adequacy in terms of precision or accuracy. A goodness-of-fit assessment was reported as part of PCFA; this section reports specifically on the generated sensitivity and specificity data for SPUR-27 using both the original cut-off score of >80% and the newly determined cut-off score of ≥87%. The MPR was included in the analysis for a

comparison of MA measures across the study cohort (Table 4.11). The results demonstrated that the SPUR-27 scoring system with the 87 cut-off had sensitivity and specificity >70.0%. The original SPUR-27 and MPR reported very low sensitivity (<50%) but very high specificity (>90%). The study also reported the predictive values (+/-) for the different models. Overall, SPUR-27 with the 87-cut-off score provided the most consistent scores across all the outcomes that were examined and could therefore consistently identify adherent and non-adherent patients.

Table 4.11 - Tests for Model Adequacy

	SPUR-27	SPUR-27 (87 Cut-off)	MPR
Sensitivity (%)	43.8%	70.3%	39.1%
Specificity (%)	97.2%	80.6%	91.7%
Positive Predictive Value (%)	49.3%	60.4%	45.8%
Negative Predictive Value (%)	96.6%	86.5%	89.3%

4.4 Discussion

This Chapter sought to summarise the psychometric properties of SPUR-27 with the aim of demonstrating the cross-cultural validity of the model in a new sample population of people living with COPD. The findings provide strong early evidence of validity for SPUR-27 in this cohort.

4.4.1 Model Structure & Goodness-of Fit

Similarly to VMATT2, a bespoke approach to model validation was developed and implemented using components of the COSMIN criteria, FDA PRO guidance and previous validation studies with a focus on cross-cultural validity.[186,187] An initial assessment of the

factorial structure of SPUR-27 in a new sample population was conducted using EFA that provided an 8-factor solution. Further exploration of the model and trimming of items with unsatisfactory loading produced a rotated solution that was incongruent with the previous SPUR-27 model. For example, two factors were identified with only two items each. Factors with ≤2 items are at risk of instability, particularly with smaller sample sizes, which was the case for this study.[369] To address this and explore an alternative factorial structure, an EFA with seven fixed factors was performed, which led to an improved rotated solution. Notably, the new structure contained one factor (Factor 7) with only two items, however these items were strongly and suitably loaded (>0.5).[369,370]

Given the limited prior testing of the SPUR-27 model, PCFA was implemented as an interim approach before CFA to provide further evidence of structural validity within the new sample population.[355,356] The fit indices, including NFI, TLI, CFI, and RMSEA, all exceeded the expected thresholds (>0.9 for NFI, TLI, and CFI, and <0.08 for RMSEA), which indicated good factor-structure fit for the 7-factor solution.[186,357,358] However, as described in the results, there were differences in item-factor loading between the 7-factor solutions identified in VMATC *vs* VMATT2. This incongruence may in part be explained by the smaller sample size attained for this study. As described by Costello and Osborne[369] "more is better" when it comes to sample sizes in factorial analysis. Smaller samples may lead to poorly generalisable or replicable results, which are reflected as unstable/inconsistent factors between populations even when alternative evidence of psychometric properties e.g., factor loadings >0.5, are reported. Alternatively, this finding may be indicative of inherent cross-cultural differences in the SPUR model between samples living with T2D and COPD. To assess these differences, the COSMIN criteria recommend methods such as MGCFA, Differential Item Functioning (DIF) or regression analyses.[186] However, neither multiple groups nor a minimum 'adequate'

sample of >100 participants were recruited for this study, hence these analyses were not performed. Moreover, while this approach is recommended, adoption of these techniques is seldom reported with most studies opting for methodologies that focus on other validity criteria e.g., factorial structure, reliability, convergent validity.[371–374] As discussed in previous Chapters, the complexity and time-investment associated with frameworks such as COSMIN may limit their application in research, particularly in relation to clinical practice settings where a more pragmatic approach is often sought.[243,265] As such, while definitive cross-cultural validity of SPUR-27 in this population cannot be assumed based on the results described above, there is a clear rationale for validity based on other psychometric properties for the model.

4.4.2 A Construct in Question: Reflecting on Hypotheses Testing, Reliability, Convergent, Concurrent, & Known-Group Validity

In contrast to the multidimensional assessment of construct validity explored in VMATT2, this study focused on a comprehensive assessment of psychometric properties including a priori hypotheses testing, reliability, convergent, concurrent, and known-group validity to inform the overall construct validity of the SPUR-27 model in this population. Convergent validity was explored between SPUR-27 and the previously validated IAS, which demonstrated a moderate (>0.6) and significant association between both measures.[308]

Encouragingly, unlike the discrepancies observed with factorial analysis, the reliability analyses conducted within VMATC reported similar results to those in VMATT2. The internal consistency estimates (α) for SPUR-27 as a total model were very strong (>0.8) without exceeding the threshold for potential item redundancy (>0.9) or the need for a shorter scale.[359,375] When compared to the original validation scores of the IAS, SPUR-27 demonstrated a greater internal consistency estimate (0.89 *vs* 0.83) and similar correlations

with an objective MA measure (ρ=0.30 *vs* 0.35), such as MPR.[191] Comparable α values (0.7-0.9) have been reported for several other similar PROMs (and their relevant factors/subscales) of MA related behaviour in patients living with COPD e.g., the Turkish version of the BeMQ, with a range of internal consistency estimates (0.682-0.832).[374] Typically, α>0.7 is used as an adequate cut-off for internal consistency.[265,359] SPUR-27 observed three Factors with α<0.7 (Factors 2, 5, & 7). These factors reported some of the fewest items per factor, which may have been a contributing factor in addition to the lower sample size.[218] While these results do not immediately preclude these factors/subscales from interpretation based on their internal consistency estimates alone, they do suggest that further investigation and caution when implementing the results of these subscales is warranted.

The effects of external factors, including the Covid-19 pandemic, had an impact on not only recruitment (and potentially analyses derived from the sample size) but also the interpretation of concurrent validity in this and previous studies.[278] Previous studies have reported a tendency for over-estimation of adherence with the MPR methodology, while this is likely the case here, the current study observed a weak significant correlation between SPUR-27 and MPR providing evidence of concurrent validity.[158,278] Interestingly, this finding contradicts previous work that found no significant correlation between refill adherence (using MPR and other similar methods) and the MARS tool, which has previously been implemented in populations diagnosed with COPD.[376–379] The VMATC study did not provide pre-pandemic data on MPR, the overall MA for the cohort using this method was high (72%) when compared to IAS (36%) and SPUR-27 (42%). Exploring other reports of MPR implementation during the Covid-19 pandemic identified discrepancies. An Italian population study of patients diagnosed with Multiple Sclerosis (MS) that used MPR to monitor changes in MA to Disease-Modifying Therapies (DMTs) throughout the pandemic, found that DMT

adherence dropped significantly in the MS cohort during the first 4-months of the pandemic (2020) compared to previously reported data from 2019 (57.0% *vs* 67.1%).[380] Conversely, an Australian study implemented a similar methodology for assessing anti-retroviral MA among People Living with HIV (PLWHIV) and reported an increase of 8% when comparing data from 2019 to 2020.[381] Notably, while all three studies (including VMATC) reported the use of direct medication delivery to patients during the pandemic, the original providers of medication differed from community pharmacies (UK), MS outpatient clinics (Italy), and sexual health centres (Australia). One may therefore surmise in the absence of more granular evidence of MPR reporting practices that several factors including the healthcare setting, potential systems used for collecting and determining MPR, and the clinical condition of interest may all have an impact on 'objective' MA data. These findings reaffirm the need for a more multifaceted approach to exploring MA and related behavioural determinants.[174,382]

Hypotheses testing was implemented to explore other behavioural determinants such as socioeconomic status, comorbidity burden, and polypharmacy on MA in COPD, as the relationship between these variables are previously well documented.[103,383–386] However, among UK populations diagnosed with COPD, the specific relationship between income and MA is not well-established. VMATC identified a significant positive correlation between income and MA using SPUR-27. Previous discussions on income and MA have focused mainly on US populations with a paid/insurance-based healthcare model, where low-income is unsurprisingly associated with poor MA in patients with COPD.[387,388] While UK data are limited, similar findings have been reported among Danish populations whereby there is a similar healthcare model to that used in the UK.[386] Moreover, the link between income and general population health across the globe has been established providing further evidence to the assumption that more affluent populations are more likely to take their medicines and in

turn, report greater health outcomes.[389] It was also predicted that MA would increase with age and decrease with an increasing number of comorbidities and prescribed medicines. While the bivariate correlations for these relationships matched predicted effect directions, the findings were not significant. Vetrano *et al*[383] highlight that for stable convergence of correlations that a sample size of approximately 250 participants should be used. As stated previously, Covid-19 was a limiting factor to recruitment, hence only a sample of 100 participants were included in the study. Therefore, in this respect the ability to detect correlated sample effects with methods such as correlation coefficients may have been limited. This limitation on sample size does not necessarily apply to all analyses given that EFA conducted with samples <50 have been successfully implemented and validated.[390] Moreover, further evidence of hypothesis testing, and specifically known-group validity was demonstrated by the Chi-Square analysis that identified a significant relationship between poor MA and increasing symptom severity. This finding supports the development of the SPUR measure to address the relationship between MA and socio-clinical factors, such as COPD symptom severity and exacerbation risk. Hence, these data support previously identified associations between MA and socio-clinical factors in COPD.[323]

Finally, known-group validity was also established for SPUR-27 when implementing a novel scoring methodology based on the ROC-AUC analysis. Adjustments to the scoring method improved the consistency of model adequacy with sensitivity and specificity values >70%. Previous pooled analyses of psychometric properties of MMAS-8 reported sensitivity and specificity as 0.43 (95% CI; 0.33, 0.53) and 0.73 (95% CI; 0.68, 0.78), respectively.[224] Arguably, MMAS-8 may be considered one of the closest PROMs in terms of being a 'gold standard' model, hence SPUR-27 as a comparator performed well in terms of sensitivity (70.3%) and specificity (80.6%). However, it is important to note that the determination of a

new cut-off value is based on this specific study population and the distribution of adherence scores within a sample of 100 participants recruited during the Covid-19 pandemic. Therefore, the cut-off value may not be applicable to other populations and iterative collection and pooled analyses of data to build upon this initial evidence of a new suitable cut-off are warranted. In summary, these psychometric properties are both encouraging and reflective of suitable construct validity, but critically there are several limitations that must also be considered when interpreting the overall findings of VMATC.

4.4.3 Limitations

As discussed in respect to several aspects of the study, the Covid-19 pandemic had a significant impact on the recruitment period, resulting in a small sample size, which may affect the generalisability of the findings. The availability of clinical data such as GOLD, MRC, and lung function tests were also limited given that these were no longer collected routinely in clinical practice, particularly outside of hospital settings, which limited some relevant socio-clinical analyses. Additionally, follow-up testing was not possible for the participants due to the risk of Covid-19, which limited the capacity to conduct a test-retest reliability evaluation. Most participants were over 70 years old, and while they were recruited by an experienced HCP and could complete the study independently, the inclusion of a validated model such as the mini mental-state examination (MMSE) would have strengthened the study's results. The MMSE would have helped to stratify different groups of patients with cognitive impairment across the study, which could then be evaluated for potential impacts on the results for SPUR. Moreover, this validated measure would ensure that the appropriate patients were excluded from the study in a systematic manner while reducing bias between HCPs identifying potential patients for the study. Although the SPUR-27 tool showed strong psychometric properties and the ability to discriminate between adherent and non-adherent

patients in this sample, the factorial structure of the tool was subject to incongruence when compared to the previously validated model in T2D. Future research should aim to expand the sample size to confirm the consistency of the factor structure and assess the measure's suitability for this validity criterion through a test-retest approach.

4.5 Conclusion

The VMATC described in this Chapter demonstrated the strong psychometric properties of SPUR-27 as a reliable tool for assessing MA in patients with COPD. This provides early evidence of its potential use in the development of tailored MA interventions, which could be applied to a variety of healthcare settings to support the early identification and characterisation of poor MA and associated risks, such as worsening COPD symptom severity. Proactive monitoring of MA and health status in these patients may also have positive health economic and -QoL outcomes, such as reducing hospitalisation or COPD exacerbations – this relationship to 'real-world application of PROMs' will be explored in more detail in Chapter 5. While this study was affected by the pandemic, which in turn limited some analyses, particularly those that may support evidence for cross-cultural validity using frameworks such as COSMIN, there were several strengths associated with the study design. For example, similarly to VMATT2, the study employed both a comparative PROM and objective measure of adherence to improve the reliability of the results in this population and to my knowledge is the first to demonstrate a holistic MA model in COPD. Additionally, significant hypotheses testing was conducted with further exploration of model adequacy and cut-off determination to build a more consistently specific and sensitive PROM of MA in this sample population.

Chapter 5: The Real-World Application of SPUR-27 as a Predictor of Admission & Early Readmission in Type 2 Diabetes

5.1 Introduction

5.1.1 Behavioural Science & Adherence – Connecting the Dots

Chapter 1 introduced Haynes' and colleagues' early contributions to MA research in the late 1970s that saw wider adoption of this area of study within the field of behavioural science.[8,9] Consequently, the impact of non-adherence on clinical outcomes became increasingly recognised within clinical practice, particularly among patients diagnosed with chronic conditions.[10] A few decades, various MA interventions were developed that were later examined as part of a 1996 SR conducted by Haynes *et al.*[391] The review identified various interventions integrated within Randomised Control Trial (RCTs) that included instructional pamphlets, counselling on the need to take medicines, warnings on adverse effects, reduced dosing regimens, self-monitoring, and even family therapy across a mix of populations diagnosed with cardiac, respiratory, neurological or infectious conditions. The researchers concluded that interventions were often complex and difficult to deliver, and ultimately had limited potential benefit based on the overall adherence of the patients enrolled in the RCTs at the time. As an aside, an interesting parallel can be drawn from the types of interventions described in the review and the theoretical underpinnings of the latter developed SPUR model.[179] For example, family therapy, counselling on the importance of MA, simplification of dosing regimens, and discussions on adverse effects are indicative of components of the Social, Psychographic, Usage, and Rational domains of the SPUR model, respectively. This perhaps reflects the shift toward describing MA in the context of TMB such as Rosenstock's[142] HBM or Ajzen's[145] TPB as just two examples that became popularised between the 1960s and 80s prior to the review conducted by Haynes *et al.*[391]

The impact of this early work to help quantify MA and understand its behavioural determinants (factors that influence an individual's decision to adopt or change a particular behaviour) is reflected in the 2001 WHO report[56] that quoted Haynes *et al*[391] with a call to action that looked to address the increasing global burden of managing chronic conditions. Specifically, the report emphasises 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. Yet despite this call to action, over two decades later, conservative estimates suggest that the cost of non-adherence to health-care systems sits somewhere between £920Mn to £224Bn across parts of Europe and the US, respectively.[55] Interestingly, the review conducted by Haynes *et al*[391] identified poor adherence among patients predominantly diagnosed with chronic cardiac, neurological, and respiratory conditions. Roughly 20 years later, a parallel can be drawn from this finding and UK estimates for the cost of non-adherence with a figure of roughly £930Mn annually that is attributed to five chronic conditions alone including T2D, COPD/asthma, schizophrenia, hypertension, and hyperlipidaemia/CAD.[392] While one might argue that MA has continued to evolve as a facet of behavioural science, these costs suggest that perhaps researchers, clinicians, and patients are yet to 'crack the code' when it comes to applying this knowledge of behaviour, particularly in those diagnosed with chronic conditions.

5.1.2 Adherence: Costs, Risks & Benefits

The enormous global costs attributed to non-adherence become less surprising when one begins to quantify the scope of the issue. This thesis has described a large range of studies, reviews, and behavioural determinants that reflect significant differences in MA between cohorts of patients that make it impossible to identify a universal rate for adherence. However, a rough assessment of the current evidence suggests that a range of approximately

30-75% of patients diagnosed with chronic conditions typically adhere to their prescribed medications.[46–51,393,394] Further evidence to support this was provided in the results of Chapter 3 & 4 that demonstrated the psychometric properties of SPUR-27 as a multidimensional model of MA. More specifically, similar findings were identified for the VMATT2 and VMATC studies that reported MA rates of 44.7% (CI; 34.8-53.4) and 37.0% (CI; 29.1-46.0), respectively. Moreover, the strong early evidence observed for the multidimensional SPUR model when compared to less holistic PROMs included in these studies is perhaps indicative of the complexity of MA behaviour. This observation in addition to the effects of factors such as clinical condition and complexity of drug therapy provide greater insight into why such large differences in MA exist not only between groups, but also between individual patients.[141] These stark differences and generally low reports of MA in chronic conditions inform the real-world implications and risk of patient behaviour on clinical outcomes that ultimately contribute to the health economic burden associated with non-adherence.

While Chapter 1 described generalised costs, such as those associated with ADRs, multimorbidity and related complications, Chapter 5 specifically considers the healthcare utilisation associated with non-adherence within the hospital setting.[72,73,395,396] Outcomes of interest include an increased risk of admission, length of stay, and overall mortality for those with poor MA.[52,54,344] In the case of admissions, previous work has identified that a large proportion of cases are preventable.[52] In 2012-2013, the cost to the NHS of patients readmitted to hospital in the UK was approximately £2.4Bn, accounting for just under a fifth of the total emergency admission cost of £12.5Bn for the same period.[397] A significant proportion of this cost is attributed to early readmissions, which occur within 30 days of a previous discharge. Since 2011, hospitals in the UK have faced financial penalties for early readmissions that were introduced with a view to discourage hospitals from attempting to free

up beds by discharging patients before they were ready.[398] One may question the relevance of MA in addressing such a broad issue such as readmission. Critically, interventions designed to specifically improve MA have demonstrated reductions in readmission risk and mortality, particularly in areas such as CVD, COPD, general medicine, post-surgical care, and mental health diagnoses.[399–403]

These results are encouraging for several reasons; however, two observations may be particularly relevant to the work conducted in this thesis. Firstly, CVD, chronic lung conditions, such as COPD, and mental health diagnoses were identified as three of the five largest contributors to non-adherence costs in the UK by Trueman *et al*,[392] which suggests the potential of MA interventions to address some of the largest areas of health economic burden associated with non-adherence. Secondly, four of the five citations that report on interventional outcomes, which include two SRs and two interventional studies, directly report on pharmacist-led interventions that had extended patient benefits after discharge by reducing morality, early readmissions (30-day), 60-day readmissions, emergency admissions, general costs in the secondary care settings and increasing overall MA.[399–401,403] Mossialos *et al*[404] describe the rapidly expanding roles of community pharmacists in recent years both in the UK, as well as other countries such as Australia, Canada, the Netherlands, and the US. The authors emphasise that with effective integration within primary care, much like the increasingly adopted pharmacy model in the UK, that pharmacists can play a pivotal role in tackling the growing burden of chronic disease and more specifically multimorbidity, which presents both the greatest health economic burden and most significant risk to patient outcomes.[37,38,40,312,405] A national examples of this is the New Medicines Service (NMS); a scheme introduced in community pharmacies in 2011 that sought to support patients with new medicines for a variety of long term conditions.[406] Elliott *et al*[395] demonstrated that the

NMS was both cost effective and had a significant positive impact on MA compared to standard pharmacy care for patients diagnosed with asthma/COPD, T2D, hypertension or those receiving antiplatelet/anticoagulant therapy. Admittedly, many of the results discussed above were modest and, in most cases, the researchers failed to discuss the sustainability of these interventions either outside the study or in the context of increasing pressures on healthcare systems. Nevertheless, the findings are positive and highlight the opportunity for on-going development.

5.1.3 The Next Step for Adherence Interventions

It seems apparent that irrespective of the setting, there is a clear role for MA and pharmacy-led interventions in supporting patients and healthcare systems. This assumption is supported by Conn and Ruppar[407] who conducted a SR and meta-analysis of 711 interventional studies with a focus on MA. The authors concluded that interventions delivered by pharmacists were the most successful in improving MA ($p<0.05$) when compared to other HCPs. However, the meta-analysis also identified only relatively small, standardised effect sizes (<0.3) for mean changes in MA post-intervention when compared with control groups. Conn and Ruppar[407] concluded that there is significant space for improvement in the development of such interventions with behavioural strategies offering the most promise for the future.

In recent years, there has been notable progress and advancements in MA interventions related to digital, mobile, and technological health innovations. These advancements include automated medication reminders, electronic cap monitors, and patient education mobile applications.[408–410] However, as emphasised by Pal *et al*,[410] such advancements are not a technological panacea given the complex relationship between MA and behavioural factors such as the impact of interpersonal relationships, communication with health-care professionals, and patient motivation/self-efficacy as just few examples of factors that impact

adherence outcomes. Moreover, there are significant interactions between MA, multimorbidity, and socio-clinical factors including disability, age, socio-economic deprivation, BMI, and self-reported education that can influence clinical outcomes such as readmission risk that need to be considered holistically when assessing the role and development of interventions.[34–36,41] One could argue that many of these interventions focus on a reactive rather than a proactive model such that they look to tackle existing poor adherence and consequently improve associated health outcomes. Yet, while the efficacy of reactive models is clear, the adage '*prevention is better than a cure*' seems strongly applicable when discussing MA given the large room for improvements in this area identified through previous research, the increasing global prevalence of multimorbidity, and stark rise in medicines use.[34–36,45,407] However, while various factors and drivers have been associated with MA and related behaviour, their use within predictive modelling has been limited by the lack of a strong predictive model.[408]

Rosen *et al*[411] conducted a study that aimed to develop a predictive model of early readmission using retrospective patient-reported MA data. These data were derived using the MMAS-4 scores reported by inpatients (n=385) in a tertiary care centre based in the US. The MMAS models are considered by some to be a quasi-gold-standard for measuring MA, concerns have been raised in relation to the internal consistency and limited predictive validity of the PROM in certain patient cohorts.[170] Furthermore, it is reasonable to question that despite the model's simplicity and ease of implementation whether sufficient behavioural data can be derived from it to inform the development of truly effective MA interventions, which are currently lacking.[23,24,407]

5.1.4 Rationale

The previous Chapters have sought to validate a holistic PROM of MA that could address issues historically associated with measuring the complex range of factors linked to adherence behaviour. The results provided strong early evidence for the psychometric properties of SPUR-27. Quantifying and understanding MA are both important precursors to the real-world application of such models that can be utilised to improve patient health outcomes through tailored interventions. While various interventions to address MA exist, there are significant limitations and room for improvement in both their development and delivery. This may be particularly true for predictive models of MA that can support the identification of preventable health outcomes and related costs, such as early readmission. It is hypothesised that as a multidimensional model that encompasses a wide array of behavioural determinants, SPUR-27 will have greater predictive capability than other PROMs in identifying such risks in patients living with chronic conditions, such as T2D.

5.1.5 Aims & Objectives

This study aimed to evaluate the predictive capability of the SPUR-27 model in identifying risks associated with poor adherence, including general admission and early readmission risk in the hospital setting. The objectives for this chapter are outlined below:

- To examine real-world evidence for SPUR and the association to clinical outcomes such as general admission and early readmission risk in patients living with T2D
- To evaluate other socio-demographic/clinical determinants of admission/readmission risk among hospital patients diagnosed with T2D
- To compare the predictive capability of admission/early readmission of SPUR to other PROMs of adherence and related behaviours in patients living with T2D

5.2 Methods

5.2.1 Study Design

This study, titled ‘VMATT2 Readmission’, was conducted using an observational cohort methodology to elicit data from a secondary phase of the VMATT2 study with a view to explore the relationship between SPUR-27 and admissions and early readmissions in people living with T2D. Data were derived from the group of participants (n=200) who were previously recruited from Kingston NHS Foundation Trust for VMATT2. Observational cohort data were collected over a 12-month duration, comprising hospital admission data both six months prior to and after participation in the original VMATT2 cross-sectional phase. The study was designed, delivered, and reported in line with the STROBE cohort guidelines.[412]

Recruitment for the original VMATT2 study cross-sectional phase began in January 2020, with the final participants being recruited in October 2021. As a result, the total observational period for data collection spanned from July 2019 to March 2022. The original PIS and consent form provided for VMATT2 provided a relevant outline on the follow-up data collection phase. Notably, the consent form contained a dichotomous statement relating to consent for follow-up data collection, where participants could opt out of the observational study. At the time of recruitment, 100.0% (n=200) of VMATT2 participants provided consent for inclusion in the observational phase (VMATT2 Readmission) that provided the total sample size for the study.

5.2.2 Data Collection

Observational data were obtained from the Trust's EHR (iCARE) and handled in accordance with the Trust's data protection and patient confidentiality policies, in addition to the General Data Protection Regulation (GDPR) enacted in 2018. Specific participant data was identified using the participant’s NHS number that was declared after completing the consent form.

When entered into the EHR, the NHS number was linked to the participant's care record at the Trust, which was able to provide a longitudinal record of inpatient and outpatient activity. Moreover, the EHR was able to provide exact dates for inpatient admissions that could be used to 1) confirm that the admission(s) fell within the 12-month observational period and 2) could also be used to determine the total number of early readmissions by comparing admissions <30 days apart. Planned admissions, such as elective surgical procedures, were included as an admission in the analyses. The decision to include planned admission was made on the basis that early readmissions may occur following a planned admission. Hence, capturing this data would provide a more comprehensive view of all admissions, including unplanned, which could then be differentiated from early admission as part of the analysis. All outpatient activity was excluded from the analysis. Other sources of data used to inform the modelling for this study were derived from the previously completed SPUR-27 questionnaires, including the socio-clinical questions and other PROMs included in the collated self-reported questionnaire for VMATT2.

5.2.3 Sample Population

As this study collected data on previously recruited patients from VMATT2, the inclusion and exclusion criteria for this phase are identical to those outlined in section Chapter 3, Section 3.4.1.1b.

5.2.4 Model Outcome Variables

VMATT2 Readmission focused on several outcome variables of interest, including: the number of admissions within the 6-month period before and after completing the SPUR-27 tool, as well as the number of early readmissions during the total observational period. To explore best model fit and to understand which model may provide the most clinical insight, admission data were collected as count data e.g., the total number of admissions/early

readmissions, and recoded into a dichotomous outcome e.g., did the participant have an admission/early readmission. The primary variable assessed in the model was MA, which was derived from the SPUR-27 tool. The previously integrated PROMs (MARS, BeMQ, DTSQ) for VMATT2 were included in the modelling.[189,190,413] The comparator PROMs were utilised as benchmarks in this model to explore specific domains of MA behaviour and overall treatment satisfaction in predicting the risk of admission among people living with T2D. Furthermore, the two previously integrated objective measures, MPR and HbA_{1c}, were also included in the analysis.

Additionally, several covariates of interest were considered, including age, ethnicity, gender, level of education, income, BMI, socio-economic deprivation, the number of prescribed medicines for T2D, and the number of medical conditions. Data pertaining to medicines prescribed for other conditions or medication complexity/burden were not collected as part of this study. The socio-economic deprivation data were derived by collating the participant's residential postcode at the time they completed the original SPUR-27 questionnaire for the VMATT2 study. These postcodes were collated and added to the Ministry of Housing, Communities and Local Government online calculator that reports the English indices of deprivation, which were most recently updated in 2019, for small areas known as Lower Super Output Areas (LSOAs).[414] The result is referred to as the IMD, with scores from either 1-1000, or more commonly reported as a decile (1-10), with 1 reflecting the most deprived and 10 reflecting the least deprived area based on factors such as local income, employment, crime, and health as a few examples. Covariate data were collected from a range of sources including the socio-demographic questions in the VMATT2 questionnaire, the Trust's EHR, or the SCR, where relevant clinical data e.g., prescribed medicines/diagnosed comorbidities, could not be derived from the EHR.

Ethical approval for the original VMATT2 study was provided in December 2019, with data collection starting in January 2020. These dates were prior to the onset of the Covid-19 pandemic in March 2020; hence Covid-19 was not originally described as a covariate in the study protocol. However, it was agreed among the research team that a Covid-19 diagnosis within the 12-month observational period should also be recorded and incorporated into the model. Approval was sought from the local research team at Kingston Hospital who advised that Covid-19 would be considered as a comorbidity, hence no additional ethical applications were sought for this amendment to data collection. However, given the unique nature of Covid-19 diagnoses among not only the general population, but also patients visiting hospital and specifically those with T2D, these data were treated as a separate variable for the model. Similarly to the previously described covariates, data for Covid-19 diagnoses were derived from either the Trust EHR or SCR.

5.2.5 Data Analysis

Descriptive data were analysed using SPSS version 26.0 for Windows. Continuous data are expressed as a mean (x) and SD. Categorical data are reported as sample number (n) and percentage (%). Following a consultation with a statistician, for modelling count outcomes, either a Poisson or negative binomial model was employed, with the selection of the appropriate model type determined by Akaike's Information Criterion (AIC). Potential non-linear effects were modelled as fractional polynomial or restricted cubic spline terms. The final model specifications were further evaluated using a link test. For binary outcomes, logistic regression models were utilised, incorporating the same set of covariates. Due to the relatively small sample size in this study, Firth's penalized maximum likelihood estimator was employed, known for its "remarkably stable performance."[415,416] Model goodness-of-fit was assessed using Pseudo R2, with McFadden's Pseudo R2 used for count outcome models

and Tjur's Pseudo R2 used for binary outcome models. In addition, for binary outcome models, metrics such as the area AUC-ROC and calibration plots were generated to evaluate the models' discrimination ability and calibration. The statistician provided support on the development of the regression and calibration models described in this Chapter. The thesis author was responsible for all other analyses including the assessment of admission characteristics, PROM data, and socio-clinical characteristics. Moreover, they were also responsible for the interpretation of both the calibration plots regression models, which included exponentiation of the count model coefficients to provide incident data for outcomes of interest.

5.3 Results

5.3.1 Study Sample Characteristics

The sociodemographic data encompassed the entire cohort that was previously recruited during the VMATT2 cross-sectional study (n=200) with a 100.0% response rate. Participant age, education, and income were collected and presented in Table 5.1. The modal age group was 70-79 years (n=74, 37.0%), accounting for over a third of the cohort. Education level was predominantly reported as GCSE levels or equivalent, representing 42.5% (n=85) of participants (n=85). Nearly three-quarters of the participants stated that they were retired (n=146, 73.0%). Participants identifying as female represented 36.0% (n=72) of the cohort. Most participants were white (n=152, 76.0%). BMI data were available for all participants (mean ± SD, 28.4 ± 5.5) and indicated that a large proportion of participants were above their recommended weight. A considerable proportion of participants (n=124, 62.0%) did not meet the HbA_{1c} target of ≤7.0% (53 mmol/mol). On average, participants were prescribed 1.9 ± 0.9 antiglycaemic agents and had 6.6 ± 2.7 diagnosed comorbidities. The modal IMD decile was 9, indicating a relatively affluent cohort based on the level of deprivation associated with

their residential postcode during the observational period. The mean ± standard deviation IMD rank was 7.3 ± 2.2.

Table 5.1 – Study Sample Characteristics

Parameter	Number (n,%)	Mode (mean±SD, range)
Age		70-79
18-29	0, 0%	
30-39	5, 2.5%	
40-49	5, 2.5%	
50-59	19, 9.5%	
60-69	28, 14.0%	
70-79	74, 37.0%	
80+	69, 34.5%	
Gender		Male
Male	128, 64.0%	
Female	72, 36.0%	
Other	0, 0%	
Ethnicity		White
White	152, 76.0%	
Black	6, 3.0%	
Asian	30, 15.0%	
Mixed	3, 1.5%	
Other	9, 4.5%	
Income		Retired
<£14999	7, 3.5%	
£15000-£24999	7, 3.5%	
£25000-£34999	7, 3.5%	
£35000-£44999	4, 2.0%	
£45000-£54999	0, 0%	
£55000-£64999	0, 0%	
£65000-£74999	1, 0.5%	
>£75000	6, 3.0%	
Unemployed	22, 11.0%	
Retired	146, 51.9%	
Education		GSCE or equivalent
No formal education	22, 11.0%	
GCSE or equivalent	85, 42.5%	
A-Level or equivalent	34, 17.0%	
Bachelors degree or equivalent	43, 21.5%	
Post-grad degree or equivalent	11, 5.5%	
Other	5, 2.5%	
Socio-Clinical Factors		
BMI (kg/m^2)	200, 100%	(28.4 ± 5.5, 14.7-47.8)
HbA_{1c} (%, mmol/mol)	200, 100%	(7.7% ± 2.1%/60.2 ± 16.3, 28.0-107.0)
Number of antiglycaemics	200, 100%	1 (1.91 ± 0.9, 1-4)
Number of conditions	200, 100%	4 (6.6 ± 2.7, 2-15)
IMD (Decile)[a]	200, 100%	9 (7.3 ± 2.2, 2-10)

Notes: [a]IMD deciles range 1-10, with 1 being the most deprived and 10 being the least deprived

5.3.2 Admissions Analysis

All participants (n=200, 100.0%) had retrospective admission data available *via* the EHR (Table 5.2). However, for the prospective data set covering the 6-month period following the completion of the SPUR-27 questionnaire, only a sample of 190 participants was utilised due to participant mortality before discharge or missing data from the EHR (n=10). Throughout the observational period, a total of 425 admissions were documented. Among these admissions, 254 (n=254/425, 59.7%) were classified as early readmissions. Early readmissions were observed in a total of 98 participants, resulting in a 12-month early readmission rate of 49% (n=98/200) for this cohort. In the 6 months prior to completing the SPUR-27 questionnaire, more than half the participants (n=103, 51.5%) had ≥1 recorded admission. Similarly, during the 6-month follow-up period, 56.8% (n=108) recorded ≥1 admission. Overall, 71% (n=142) of the cohort experienced ≥1 admission within the 12-month observational period, with 69% of these cases (n=98/142) having ≥1 early readmission recorded.

Table 5.2 – Admissions & PROM Results

Variable (n)	**Range**	**Mean ± SD**	**Sum[b]**
Number of admissions in the previous 6 months (n=200)	0-12	1.1 ± 1.7	214
Number of admissions in the following 6 months (n=190)	0-11	1.1 ± 1.3	211
Number of early readmissions during the observational period (n=200)	0-22	1.3 ± 2.5	254
MARS Score (%[a], n=200)	20.0-100	78.3 ± 16.8	
BeMQ-S Score (%, n=200)	40.0-100	77.8 ± 12.1	
BeMQ-G Score (%, n=200)	22.5-100	66.2 ± 16.4	
DTSQ Score (%, n=200)	0-100	81.2 ± 16.8	
SPUR-27 Score (%, n=200)	55.1-98.2	80.9 ± 9.4	
MPR Score (%, n=200)	15.6-100	88.7 ± 19.8	

Notes: [a]PROM scores were converted to percentages as with previous Chapters for ease of comparison when discussing relative levels of adherence/behavioural scoring between the different tools;[b]The Sum columns is indicative of the total number of events across the study cohort

To evaluate MA and related behavioural determinants as well as overall treatment satisfaction, average scores for the PROMs originally included in the VMATT2 data collection phase were converted to percentages for comparison using the commonly assigned cut-off score of 80% for the objective MPR measure, among other models.[291] The most notable contrast in scores was observed between MPR and BeMQ-G scores (Figure 5.1). Among the participants, 80% (n=160) achieved scores ≥80% for MPR, while only 22% (n=44) achieved scores ≥80% for BeMQ-G. As for the multifactorial SPUR-27, 58% (n=116) of participants achieved scores ≥80%. These findings align with previous reports of MA among cohorts of individuals living with chronic conditions, including T2D. Notably, SPUR-27 was the only model to report neither a ceiling nor floor effect (Table 5.2) with this 200 participant sub-sample of the original VMATT2 cohort (n=378).

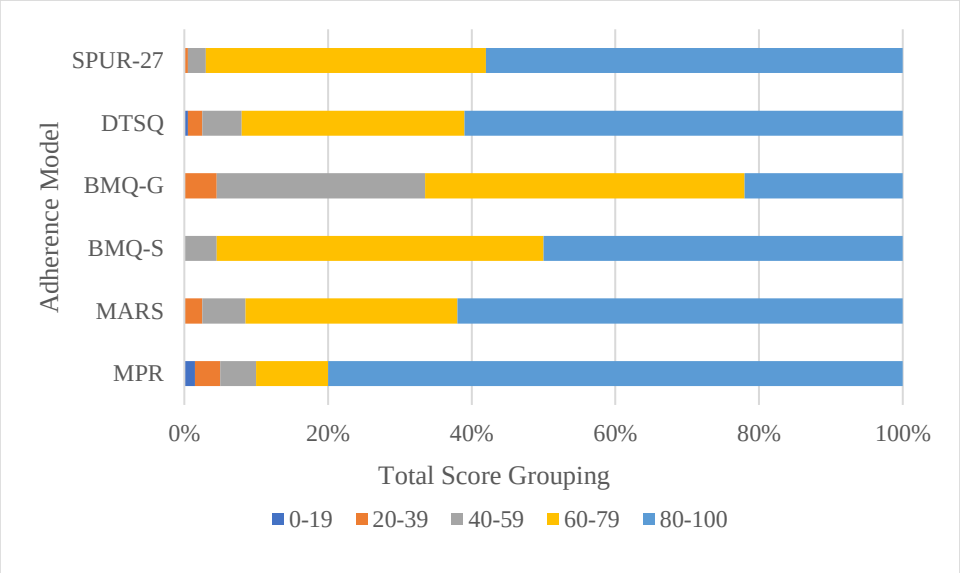


Figure 5.1 Percentage Scoring Proportions by Quintiles for PROMs & MPR

5.3.3 Regression Modelling & Calibration Plots

The principle focus of VMATT2 Readmission was to explore the relationship between SPUR-27 scores and the main outcome variables (admission and early readmission). To

minimise the impact of confounding variables, other factors were adjusted in the respective count or binary regression models and therefore were exploratory in nature. The modelling results, including coefficients and their 95% CIs, are presented in Tables 5.3 and 5.4 for admissions and early readmissions, respectively. For count models, the exponentiated coefficient also represents the incidence ratios (IR). For example, Table 5.3 demonstrates that a one unit increase in SPUR-27 (Coefficient=-0.024; 95% CI -0.045, -0.003) is associated with a decrease in the number of admissions by a factor of 0.98 (IR=0.98; 95% CI 0.96, 1.00). In simpler terms, a higher SPUR-27 score (indicating increased adherence) was predictive of a lower number of admissions during the follow-up period. For all binary models, only coefficients and their respective 95% CI are reported. For all count models, the IR and their respective 95% CI are reported. Furthermore, only IRs for significant factors have been reported.

5.3.3.1 Negative Predictors of Admission Risk (Count Model)

Similarly to SPUR-27, two other factors were found to be significantly negatively associated with an admission, which included higher MPR scores (IR=0.99; 95% CI 0.98, 1.00) and a positive Covid-19 diagnosis within the 6-month period before study completion (IR=0.65; 95% CI 0.43, 1.00). For further clarification using the latter result as an example, an IR of 0.65 indicates that for those diagnosed with Covid-19 prior to study completion, the incidence of admissions was 35% lower in this group compared to those that did not report Covid-19 prior to study completion.

5.3.3.2 Positive Predictors of Admission Risk (Count Model)

Several factors were found to be significantly and positively associated with admissions. These factors included age ≥80 years (IR=5.18; 95% CI 1.01, 26.55), GCSE level education or equivalent (IR=2.11; 95% CI 1.15, 3.87), the number of diagnosed medical conditions

(IR=1.07; 95% CI 1.01, 1.13), a positive Covid-19 diagnosis during the 6-month follow-up period (IR=1.83; 95% CI 1.11, 3.02), a higher BeMQ-S score (IR=1.02; 95% CI 1.00, 1.04), and a higher HbA_{1c} (IR=1.02; 95% CI 1.01, 1.03).

Table 5.3 - Regression Model Results for Admissions in the 6-month Follow-up Period

	Count Model		Binary Model	
	Number of admissions in following 6 months		Did the patient have an admission within the following 6 months?	
Variable	Coefficient	95% CI	Coefficient	95% CI
Age (30-39)	ref.		ref.	
40-49	1.544	[-0.168, 3.256]	1.613	[-1.727, 4.952]
50-59	1.158	[-0.470, 2.786]	1.114	[-1.895, 4.124]
60-69	0.685	[-0.868, 2.239]	0.735	[-2.156, 3.625]
70-79	1.15	[-0.529, 2.829]	1.088	[-1.918, 4.094]
80+	1.645[a]	[0.012, 3.279]	1.777	[-1.301, 4.856]
Education (No formal education)	ref.		ref.	
GCSE or equivalent	0.747[a]	[0.141, 1.354]	0.822	[-0.322, 1.966]
A-level or equivalent	0.138	[-0.590, 0.865]	-0.066	[-1.369, 1.237]
Bachelors degree or equivalent	0.533	[-0.200, 1.266]	0.516	[-0.742, 1.774]
Post-graduate degree or equivalent	0.578	[-0.306, 1.463]	1.005	[-0.762, 2.771]
Other	0.298	[-0.761, 1.358]	0.53	[-1.768, 2.829]
Income ≤£14999	ref.		ref.	
£15000-£24999	-1.188	[-3.086, 0.711]	0.282	[-2.905, 3.469]
£25000-£34999	-0.397	[-2.074, 1.279]	0.847	[-1.535, 3.230]
£35000-£44999	0.45	[-1.386, 2.287]	1.186	[-1.204, 3.577]
£65000-£74999	-1.262	[-2.897, 0.373]	-1.648	[-5.859, 2.563]
≥£75000	0.632	[-1.146, 2.410]	1.041	[-1.561, 3.644]
Unemployed	-0.067	[-1.574, 1.439]	0.383	[-1.673, 2.438]
Retired	-0.149	[-1.639, 1.341]	0.393	[-1.363, 2.149]
Gender (male)	ref.		ref.	
Female	-0.215	[-0.559, 0.130]	-0.155	[-0.854, 0.545]
Ethnicity (White)	ref.		ref.	
Mixed/Multiple Ethnic Groups	-0.261	[-1.227, 0.705]	1.876	[-1.426, 5.179]
Asian/Asian British	0.447	[-0.021, 0.914]	0.452	[-0.573, 1.477]
Black/African/Caribbean/Black British	0.793	[-0.727, 2.312]	-0.228	[-2.778, 2.322]
Other Ethnic Groups - Please Specify	-0.108	[-0.810, 0.595]	-0.452	[-2.060, 1.156]
Socio-clinical/PROMs				
BMI	-0.019	[-0.051, 0.013]	-0.024	[-0.088, 0.039]
Number of Antidiabetic Medications	0.069	[-0.141, 0.279]	-0.106	[-0.522, 0.309]
Number of Medical Conditions	0.071[a]	[0.014, 0.128]	0.193[b]	[0.061, 0.324]
IMD Decile	0.068	[-0.020, 0.156]	0.181[a]	[0.023, 0.339]
Covid within 6 months pre-admission?	-0.425[a]	[-0.847, -0.004]	-0.333	[-1.340, 0.674]
Covid within 6 months post-admission?	0.605[a]	[0.106, 1.105]	1.47	[-0.194, 3.134]
MARS Score (%)	0.022	[-0.116, 0.159]	0.161	[-0.104, 0.426]
BeMQS Score (%)	0.021[a]	[0.001, 0.040]	0.019	[-0.017, 0.054]
BeMQG Score (%)	-0.005	[-0.019, 0.009]	-0.004	[-0.029, 0.021]
DTSQ Score (%)	0.001	[-0.010, 0.011]	-0.003	[-0.028, 0.022]
HbA_{1c}	0.017[b]	[0.006, 0.028]	0.027[a]	[0.003, 0.050]
Medication Possession Ratio (%)	-0.013[c]	[-0.021, -0.005]	-0.026[a]	[-0.049, -0.004]
SPUR-27 Score (%)	-0.024[a]	[-0.045, -0.003]	-0.048[a]	[-0.094, -0.003]
Constant	-1.706	[-4.080, 0.668]	-1.264	[-6.176, 3.647]
Observations	190		190	
[d]Pseudo R^2	0.139		0.234	
AIC	544.65		185.179	
AUC			0.798	

Notes: [a]$p<0.05$, [b]$p<0.01$, [c]$p<0.001$; [d]Pseudo R^2: McFadden's for count outcomes and Tjur's for binary outcomes
Abbreviations: BMI, body mass index; IMD, index of multiple deprivation; AIC, Akaike information criterion; AUC, area under the curve

5.3.3.3 Predictors of Admission Risk (Binary Model)

When modelled as a binary outcome (Coefficient; 95% CI), a higher HbA_{1c} (0.027; 95% CI 0.003, 0.050), a lower SPUR-27 score (−0.048; 95% CI −0.094, −0.003), a lower MPR score (−0.026; 95% CI −0.049, −0.004), and a higher number of diagnosed medical conditions (0.193; 95% CI 0.061, 0.324), remained significantly associated with an admission (Table 5.3). A higher IMD decile, which reflects lower deprivation scores, was an additional factor that was positively and significantly (0.181; 95% CI 0.023, 0.339) associated with an admission in the binary model.

5.3.3.4 Negative Predictors of Early Readmission Risk (Count Model)

Several factors had an inverse relationship with early readmissions (Table 5.4). These included patients identifying as female (IR=0.52; 95% CI 0.33, 0.83) and those with an annual income of £65,000-£74,999 (IR=-16.248; 95% CI -18.866, -13.630) being less likely to be admitted. It's important to note that the coefficient for the income category £65,000-£74,999 is unusually large (-16.248) for the count outcome, suggesting an unrealistically large effect. The main variable of interest in this study is the SPUR-27 score, and the purpose of adjusting for other factors is to mitigate confounding effects, thus making them exploratory in nature. Moreover, the number of patients in each income category is extremely low e.g., there is only one patient with an income of £65,000-£74,999. As a result, the estimated effect becomes more unreliable, particularly since this participant happened to have zero early readmissions, which may artificially inflate the result. To better understand the impact of income as a covariate, a larger sample size is required.

5.3.3.5 Positive Predictors of Early Readmission Risk (Count Model)

A Covid-19 diagnosis during the 6-month follow-up period was the only factor found to demonstrate a positive association with early readmission risk in the count model (IR=2.90; 95% CI 1.62, 5.16).

5.3.3.6 Predictors of Early Readmission Risk (Binary Model)

A Covid-19 diagnosis during the 6-month follow-up period remained a significant factor (Coefficient=1.692; 95% CI 0.464, 2.919) associated with early readmission in the binary model. Other significant covariates included patients reporting either a GCSE education (1.257; 95% CI 0.054, 2.460) or an A-level (or equivalent) education (1.445; 95% CI 0.126, 2.763). The SPUR-27 score was the only factor inversely associated with the binary outcome (-0.051; 95% CI -0.094, -0.007), indicating that patients with higher SPUR-27 scores (higher expected MA), were less likely to experience an early readmission during the observational period.

Table 5.4 - Regression Model Results for Early Readmissions in the 6-month Follow-up Period

	Count Model		Binary Model	
	Number of early readmissions in the observational period		Did the patient have an early readmission during the observational period?	
Variable	Coefficient	95% CI	Coefficient	95% CI
Age (30-39)	ref.		ref.	
40-49	0.82	[-1.223,2.862]	-0.03	[-3.512,3.452]
50-59	1.066	[-0.879,3.011]	-0.317	[-3.002,2.368]
60-69	0.046	[-1.752,1.845]	-0.85	[-3.747,2.047]
70-79	0.862	[-1.064,2.787]	-0.207	[-3.117,2.703]
80+	0.993	[-0.967,2.953]	0.112	[-2.844,3.068]
Education (No formal education)	ref.		ref.	
GCSE or equivalent	0.328	[-0.502,1.157]	1.257[a]	[0.054,2.460]
A-level or equivalent	0.428	[-0.416,1.273]	1.445[a]	[0.126,2.763]
Bachelors degree or equivalent	-0.265	[-1.189,0.659]	1.263	[-0.042,2.569]
Post-graduate degree or equivalent	0.282	[-1.042,1.607]	0.995	[-0.714,2.704]
Other	-0.036	[-1.658,1.587]	1.531	[-0.739,3.801]
Income ≤£14999	ref.		ref.	
£15000-£24999	-0.503	[-2.378,1.372]	-0.541	[-3.406,2.323]
£25000-£34999	-1.288	[-3.313,0.737]	-0.622	[-3.108,1.865]
£35000-£44999	-0.324	[-1.819,1.170]	0.592	[-1.799,2.982]
£65000-£74999	-16.248[c]	[-18.866,-13.630]	-3.813	[-8.240,0.613]
≥£75000	-0.043	[-1.518,1.432]	0.924	[-1.562,3.410]
Unemployed	-0.02	[-1.423,1.383]	-0.284	[-2.455,1.888]
Retired	-0.486	[-1.642,0.669]	-0.405	[-2.221,1.412]
Gender (male)	ref.		ref.	
Female	-0.648[b]	[-1.107,-0.189]	-0.291	[-0.962,0.380]
Ethnicity (White)	ref.		ref.	
Mixed/Multiple Ethnic Groups	-1.296	[-3.401,0.808]	-1.387	[-4.137,1.362]
Asian/Asian British	0.027	[-0.638,0.693]	0.28	[-0.720,1.281]
Black/African/Caribbean/Black British	0.221	[-1.581,2.022]	0.451	[-1.698,2.600]
Other Ethnic Groups - Please Specify	0.097	[-0.654,0.847]	0.544	[-1.078,2.166]
Socio-clinical/PROMs				
BMI	-0.003	[-0.041,0.034]	-0.013	[-0.073,0.046]
Number of Antidiabetic Medications	-0.151	[-0.413,0.112]	0.073	[-0.322,0.468]
Number of Medical Conditions	0.038	[-0.038,0.113]	0.096	[-0.027,0.218]
IMD Decile	0.065	[-0.023,0.152]	0.088	[-0.063,0.239]
Covid within 6 months preadmission?	-0.04	[-0.593,0.513]	-0.032	[-0.916,0.852]
Covid within 6 months post admission?	1.063[c]	[0.484,1.641]	1.692[**b**]	[0.464,2.919]
MARS Score (%)	0.061	[-0.118,0.240]	0.045	[-0.204,0.295]
BeMQS Score (%)	non-linear[e]		0.22	[-0.012,0.057]
BeMQG Score (%)	0.014	[-0.002,0.029]	0.007	[-0.017,0.031]
DTSQ Score (%)	-0.001	[-0.015,0.014]	0.011	[-0.013,0.035]
HbA_{1c}	non-linear[e]		0.22	[-0.001,0.045]
Medication Possession Ratio (%)	-0.005	[-0.015,0.006]	non-linear[e]	
SPUR-27 Score (%)	-0.027	[-0.057,0.003]	-0.051[a]	[-0.094,-0.007]
Constant	-5.684[a]		-3.378	
Overdispersion parameter	-0.029	[-0.454,0.397]		
Observations	200		200	
[d]Pseudo R^2	0.101		0.13	
AIC	631.302		239.686	
AUC			0.79	

Notes: [a]$p<0.05$, [b]$p<0.01$, [c]$p<0.001$, [d]Pseudo R^2: McFadden's for count outcomes and Tjur's for binary outcomes, [e]found to have a statistically significant but non-linear relationship with early readmissions

5.3.3.7 Calibration Plots

The calibration plots depicted in Figures 5.2 and 5.3 provide a visual representation of the calibration of the binary outcome models. These plots offer insights into the alignment between the predicted probabilities and the observed frequencies of the outcome (admission or early readmission). This alignment, otherwise referred to as the calibration, reflects the overall accuracy of the risk-estimation for the model.[417] Overall, the plots indicated that the models exhibit a reasonable level of calibration.

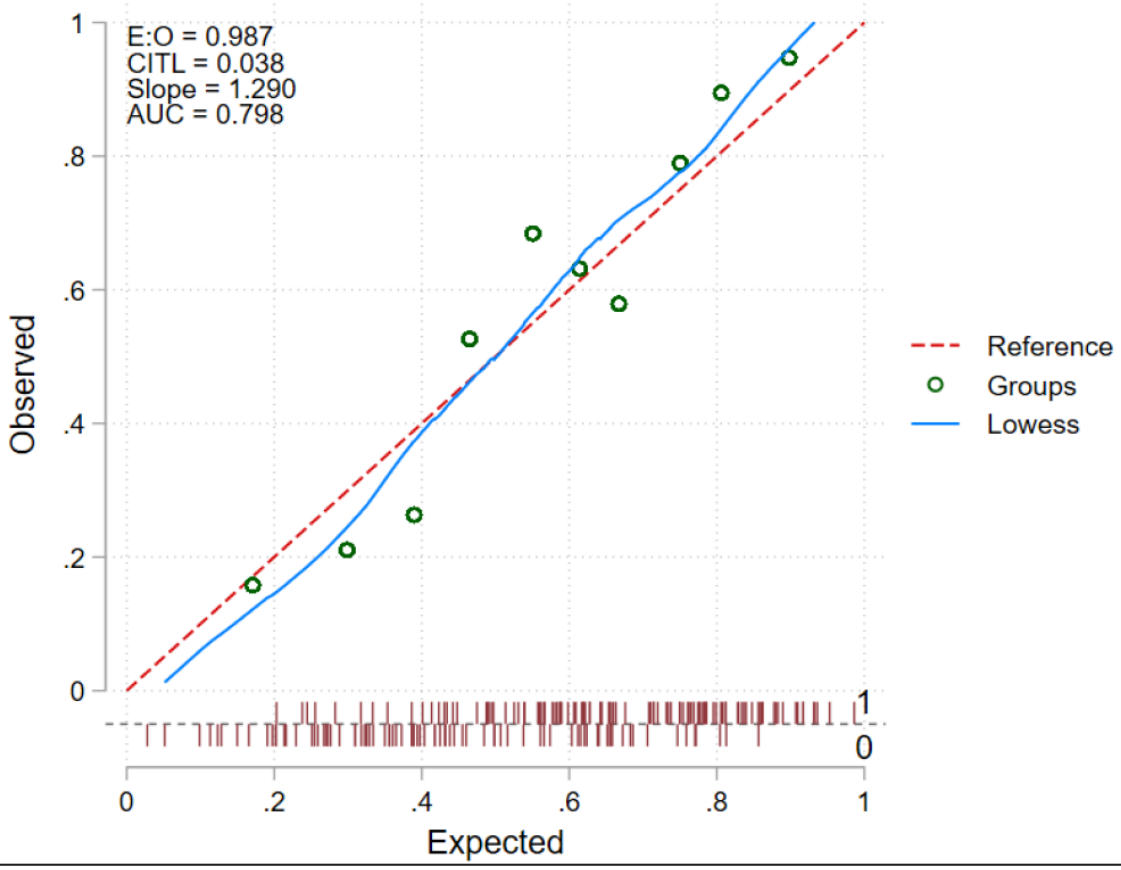


Figure 5.2 – SPUR-27 Binary Outcome Model Calibration Plot: Did the patient have an admission within 6 months post-discharge?

Notes: E:O (Best = 1); CITL (Best = 0); All circles refer to the probability groups (Best = closer to the reference line).

Abbreviations: E:O, expected: observed ratio; CITL, calibration in the large index; LOWESS, locally weight scatterplot smoothing.

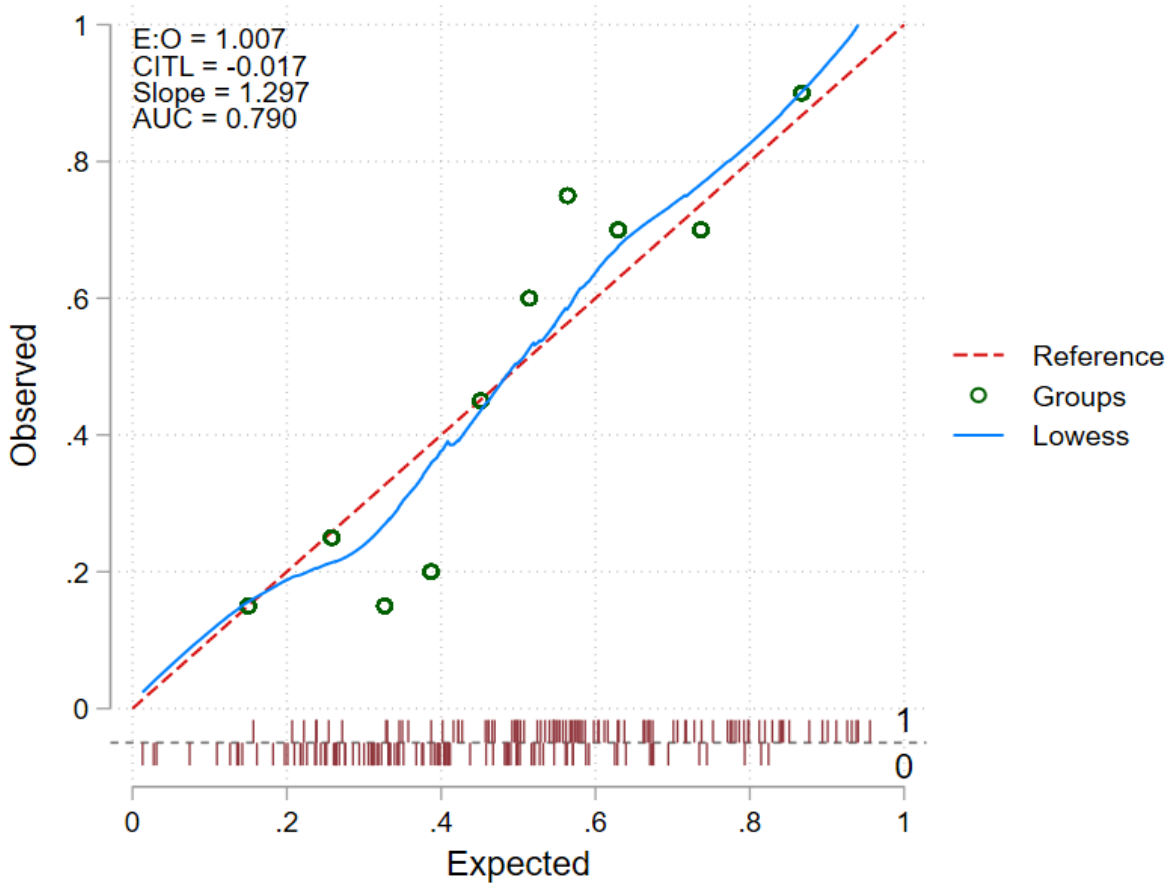


Figure 5.3 – SPUR-27 Binary Outcome Model Calibration Plot: Did the patient have an early readmission within 6 months post-discharge?

Abbreviations: E:O, expected: observed ratio; CITL, calibration in the large index; LOWESS, locally weight scatterplot smoothing.

While the plots suggest that the models are well calibrated within the data used for VMATT2 Readmission, it is important to note that additional external data are needed to validate the models more comprehensively. External validation allows for an assessment of the models' performance on new, unseen data, which is crucial to evaluate their generalisability and improve the algorithms to provide more accurate predictions, which can ultimately increase the model's reliability in future real-world applications.[416]

5.4 Discussion

This Chapter sought to develop and describe a predictive model for general admission and early readmission in individuals with T2D that incorporated SPUR-27 as a PROM of MA. Specifically, this Chapter aimed to build on previous evidence of early psychometric properties of the SPUR-27 model by exploring the real-world application of a PROM and other socio-clinical covariates associated with the risk of hospital admissions. The findings of VMATT2 Readmission offer initial evidence that supports the reliability of the model, with SPUR-27 identified as a significant predictor for both general admission and early readmission in the patient population.

5.4.1 Exploring Early Readmission Rates

During the VMATT2 Readmission observational period, a total of 425 admissions were recorded. Among these admissions, over half were categorised as early readmissions, which affected just under half of the total cohort (n=98/200). These findings produced an early readmission rate of 49% for the cohort. This rate appears to be disproportionately high when compared to early readmission rates in similar sample populations of acute surgical or medical patients, which includes cohorts affected by cardiometabolic disease with figures ranging from 7.6% to 19%.[418–424] The potential influence of Covid-19 as a contributing factor to this discrepancy was considered. Just over a fifth (22%, n=44) of the participants were recorded with a positive diagnosis during the observational period. However, when compared to other samples of patients diagnosed with Covid-19, readmission rates closer to ~7.5% are reported.[425,426] While Covid-19 was a distinguishing characteristic captured within this sample population, the large gap observed when comparing readmission rates to the wider literature suggests a more complex model of readmission risk that should reflect a range of other socio-clinical factors.

Notably, the participants included in VMATT2 Readmission were primarily older retired individuals (over 70 years old). They exhibited poor-moderate adherence to HbA_{1c} targets and their medications as indicated by a range of PROMs exploring difference behavioural determinants, and they presented with a relatively high multimorbidity burden (mean±SD comorbidities=6.6±2.7). These factors may partially justify the increased readmission rates observed in this cohort. However, it is important to comment on the general deprivation level of the cohort. The majority of participants were socio-economically affluent when using IMD deciles as an indicator. One might expect to observe a lower readmission rate given the evidence of an inverse relationship that indicates that older patients (>65) from deprived areas are more prone to hospital readmissions.[421] The very high proportion of early readmissions identified in this Chapter certainly warrants further investigation given that the case for causality can neither be attributed to poor MA alone, as identified by SPUR-27, nor any other expected predictive factor previously identified in the literature. However, this finding does perhaps highlight the need for multifactorial methods when assessing not only PROs, such as MA, but also real-world health outcomes in clinical practice.

5.4.1.1 Assessing Model Covariates for Early Readmission

A definitive explanation for the high proportion of early readmissions could not be readily supplied using the findings of the predictive model. However, the model did successfully identify several covariates associated with this outcome and general admissions. The presence of a Covid-19 diagnosis during the 6-month follow-up period was the only factor consistently linked to an increased likelihood of early readmission in both the binary and count models.

Previous studies have established that factors such as a T2D diagnoses, obesity, male gender, and being over the age of 65 are associated with a higher risk of Covid-19-related morbidity

and mortality.[425,427–430] The cohort recruited for VMATT2 Readmission predominantly consisted of males participants (64%), individuals over 65 years of age, and those classified as overweight using a BMI value >25 as an indicator. Consequently, it is not surprising that this cohort would be more susceptible to Covid-19-related complications such as morbidity and mortality, which could contribute to additional admissions or readmissions during the observational period. Further evidence of socio-demographic differences was observed when the model identified that female participants were significantly less likely to experience early readmissions. These results aligned with previous reports from both Collins *et al*[431] and Comino *et al*[432] that suggests males with T2D are more prone to overall hospitalisation and early readmission.

Unlike gender, age, and obesity, the role of patient education in admission risk in T2D is less established. However, a few studies have highlighted that participants who report being less educated experience an increased risk of early readmission.[422,423] This may in part be attributed to poorer health literacy, a greater prevalence of risk-factors for chronic conditions such as high BMI, and the association with a lower socio-economic status, which as described in Chapter 1, have all been identified as strong predictors of multimorbidity that inadvertently can contribute to a greater risk of hospital admission.[34–36,41] Specifically for VMATT2 Readmission, when compared to participants without a formal education, patients with a Bachelor's degree or higher did not observe a significantly increased risk of early readmission. However, those who either reported a GCSE or A-level equivalent education, which accounts for just less than 60% of the cohort, were significantly more likely to experience this outcome during the study. Hence, just as the broad known-group validity analyses conducted in Chapter 3 and 4 informed the SPUR-27 model, a comprehensive socio-

clinical model in addition to MA can also inform risk-based health outcome assessments such as in the case for early readmission.

5.4.2 Adherence & Admissions

In addition to socio-clinical factors, the model demonstrated evidence of the potentially critical role of a holistic MA assessment and related behavioural determinants given that SPUR-27 emerged as the only PROM that significantly predicted the likelihood of early readmission. Similarly to Rosen *et al*,[411] patients with higher levels of MA, were less likely to experience an early hospital readmission. This previous study sought to create a predictive model for early readmission using a partially comparable methodology by utilising retrospective MA data obtained from completion of the MMAS-4 by inpatients in tertiary care centres based in Los Angeles.[209] While the results provided by Rosen *et al*[411] align with those reported from VMATT2 Readmission, the implementation of the MMAS model warrants further discussion. Despite the MMAS being widely revered as a quasi-gold standard PROM for MA, particularly with the introduction of the 8-item scale, both MMAS-4/-8 have observed several limitations in terms of internal consistency, predictive validity, and CCA as documented in Chapter 2.[141,170,216,258,433] Notably, a recent SR and meta-analysis of MMAS-8 psychometric properties conducted by Moon *et al*[259] concluded that evidence for the model's ability to screen for non-adherence, which included populations diagnosed with T2D, was lacking.

Irrespective of potential issues identified with the psychometric properties of MMAS, one might also argue that the scale's simplicity does not address the numerous and complex factors underlying MA behaviour.[141] As demonstrated in this Chapter, these factors are critical considerations for comprehensive assessments of health outcomes such as admission risk. To this extent, development of a predictive model that integrates data derived from a

PROM with such a specific scope of adherence reporting may fail to fully address the holistic nature of MA behaviour and the impact on real-world outcomes. In fact, intra-population variability in PROM results as well as poorly established links to clinical outcomes were limitations identified as early as Chapter 2, which informed the SR of PROM validity (Chapter 2) and later development of a bespoke validation methodology (Chapters 3 & 4) that could provide evidence to support the real-world application of the SPUR-27 model (Chapter 5).[172,175,176] The perceived superiority of a multidimensional PROM of MA was a core hypothesis for this thesis. While neither MMAS-4 nor MMAS-8 were implemented as part of this research, evidence to support this hypothesis is perhaps offered by the fact that as previously discussed, no other validated PROM included in this study reported significant predictions for early readmission risk. Moreover, neither objective measure of adherence, MPR and HbA_{1c}, demonstrated any significant association with the outcome variable. Hence, multidimensional models such as SPUR-27 may have an increasingly important part to play as part of an interventional approach to identify and tackle early readmission risk, particularly when compared to other standard PROMs and objective measures currently implemented in clinical practice.

Much like the model for early readmission, a higher SPUR-27 score was indicative of a lower risk of general admission. However, in this model, one additional PROM (BeMQ-S), as well as MPR and HbA_{1c} were also significant predictors of the outcome. Surprisingly, a higher BeMQ-S score, which indicates that patients recognise the necessity of their medications and have lower perceived concerns about their long-term/adverse effects, was associated with admission risk. To my knowledge, there are no comparable predictive models for admission risk that have included the BeMQ-S, making direct comparisons with existing literature difficult. It was initially hypothesised that a significant inverse relationship would be

observed, considering that perceiving high necessity and low concerns about medications has been linked to improved adherence and reduced healthcare utilisation.[434] To validate this result, future studies with larger sample sizes are needed – a consideration that is further expanded in the limitations section of this Chapter.

5.4.2.1 Considerations for Covid-19

Unsurprisingly several socio-clinical factors were also predictors of general admission, including increasing age (>80 years), the presence of comorbidities, and having a General Certificate of Secondary Education (GCSE) level of education. An unexpected finding of interest was that a diagnosis of Covid-19 in the 6-month period prior to study participation was associated with a lower risk of admission. This result seems somewhat counter-intuitive to early discussions in this Chapter regarding the role of Covid-19 diagnoses in increasing admission and early readmission risk, particularly for patients with T2D. One possible explanation may be derived from a recent study by Nyland *et al*[435] that investigated the initiation of T2D treatments, including GLP-1R agonists, pioglitazone, and DPP-4 inhibitors, prior to a Covid-19 diagnosis. Notably, patients who received a GLP-1R agonist six months prior to their Covid-19 diagnosis experienced a 33% reduction in hospitalisation. Unfortunately, this study did not specifically examine the initiation of medications for participants during the observational period, therefore it's not possible to ascertain whether medicines such as GLP-1R agonists were prescribed retrospectively in this cohort. However, during the pandemic, individuals with T2D were considered "vulnerable" in terms of Covid-19. One hypothesises that it is possible that patients were more aware of their risk because of targeted public health campaigns and wider societal knowledge of the relationship between T2D and Covid-19 that may have facilitated patients to proactively seek healthcare and improve their MA. This may have been particularly true following a Covid-19 diagnosis,

which as a result could inadvertently decrease the likelihood of future hospital admissions. Certainly, this finding among others such as with the unexpected significant BeMQ-S result warrant further investigation with larger sample sizes to establish a causal relationship.

5.4.3 Calibration

Although sufficient evidence for determining the causality of some findings of the study may be lacking, VMATT2 Readmission implemented calibration as a 'key aspect of performance that is often overlooked' in predictive modelling.[416] Even when models demonstrate good discrimination, there is a possibility of unreliable risk estimates. This is an important consideration, as highlighted by Van Calster and Vickers,[436] who argue that a model with a lower AUC but better calibration might be more valuable, especially in the context of clinical decision-making where risk-estimates are employed. Both predictive models developed in this study exhibited an AUC of approximately 0.8, indicating strong discrimination, and reasonable calibration. However, it is essential to validate these models using external data for further confirmation. Nevertheless, this early evidence of discrimination and calibration is promising for the creation of a clinically relevant predictive model for patients with T2D that incorporates a multidimensional PROM of MA.

5.4.4 Limitations

While Firth's penalized maximum likelihood estimator was utilised in this study, the sample size was relatively small. To overcome this potential limitation, future external validation with a larger sample is warranted. Moreover, adjustments for multiple testing were not included at this stage of the study. This approach may be less beneficial when analyses are predominantly exploratory in nature, which was the case for VMATT2Readmission. However, multiple testing adjustments will be a valuable addition to future research given that the initial relationships between SPUR-27 and the study outcomes have been established.

It should be noted that the sample consisted of mostly affluent patients, with 78.5% (n=157) reporting an IMD decile ≥6. According to the binary general admission model, patients with a higher IMD decile (indicating less deprivation) were found to have a higher likelihood of experiencing an admission. This finding contradicts the results of the early readmission model, which observed a lower readmission risk among more affluent patients, as well as the broader existing literature.[421] Therefore, while the sample population was reflective of the local community in Southwest London, further validation should be conducted in line with recommendations for CCA as outlined in Chapter 2, 3 and 4. This may include assessing the psychometric properties of SPUR-27 and regression models of cohorts of readmitted hospital patients from more diverse socio-economic backgrounds and varying levels of deprivation. This study did not consider medicines for other chronic conditions, nor did it consider medication complexity or burden. These data have been previously implicated with differences in MA between patients. Future work should look to evaluate the relationship between SPUR and these factors as part of the predictive modelling for admission, but also more broadly on the results of SPUR as it relates to a holistic assessment of MA behaviours.

5.5 Conclusion

This Chapter presented preliminary evidence supporting the role of SPUR-27 as multidimensional PROM of MA that can reliably predict general admission and early readmission in the study population. Notably, SPUR-27 appears to outperform other PROMs and objective measures of MA in terms of its predictive capacity. This finding holds promise for future research focusing on the development of tailored intervention strategies for admission risk in patients with complex MA issues that could be identified using SPUR-27. The hope is that this early evidence of real-world application of SPUR-27 model can facilitate wider implementation across various healthcare settings such as community

pharmacies, GP surgeries, nursing homes, and domiciliary care, where HCPs can use the results to better support patients with their medicines.

Furthermore, the model identified in this study reported several other significant predictors of admission risk that have previously been associated with T2D, including age, gender, multimorbidity, and a more novel yet noteworthy factor—Covid-19 diagnoses prior to and after admission. While the relationship to the latter may require more investigation, these overall findings contribute meaningfully to the existing body of evidence and shed light on the potential link between treatment initiation for T2D, Covid-19, and reduced admission risk. Moreover, despite the small sample size, this Chapter and the VMATT2 Readmission study employed various statistical methods, including Firth's penalized estimator, to enhance both the performance and clinical relevance of the model. However, external validation of the model is necessary, along with an examination of its applicability to larger and more diverse samples of individuals living with T2D and other chronic conditions where SPUR-27 has been implemented.

Chapter 6: Conclusion

6.1 Review of the Research

A key principle underpinning this thesis is reflected in the 2001 WHO statement 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". While this statement demonstrates a clear regard for the importance of strategies that can support patients taking their medicines, advancements in this area have been arguably far less clinically impactful than those made in drug development over the last two decades.

Addressing adherence is a priority given the rapid growth in the global population, with estimates as high as 8Bn as of November 2022, in tandem with the prevalence of multimorbidity. Notably, just four major categories of chronic conditions including CVD, chronic lung conditions, cancer, and diabetes have been associated with ~60% of worldwide mortality within the last several decades. To match the changing needs of these populations, medicines use, and expenditure have also risen dramatically with an almost 10% increase (£1.9Bn) in the latter within the space of one year alone in England (2018/19 *vs* 2019/20).

Are patients taking their medicines? – This was an initial question posed by the introduction to this thesis that was met with significant evidence to suggest that the answer is much more complex than one might assume. Non-adherence has and continues to be widely recognised among people diagnosed with chronic conditions. Despite a lack of novel clinical interventions, there have been substantial developments in our understanding of TMBs that underpin specific adherence-related behaviours. From this work, PROMs have been developed with a view to measure and identify said behaviours with varying success. Limitations to the development and delivery of clinically relevant PROMs could be in part due to poor implementation of holistic models of behaviour that are hypothesised to better

assess if patients *are* taking their medicines, but perhaps more importantly, their limited ability to provide insights as to *why* patients may or may not take their medicines. At its core, this research sought to centre individual patient experience within a model of care that can address the growing burden of medication non-adherence, using SPUR as a newly developed holistic PROM.

The research was undertaken in England, with several studies conducted within Southwest London. The primary aim was to evaluate the validity of SPUR as a reliable multidimensional PROM of MA in patients diagnosed with chronic conditions, T2D and COPD, with a view to evaluate its association and application to real-world health outcomes.

Key objectives for this thesis included:

- Establishing the current practices for reporting PROMs of MA in T2D with a specific lens on understanding the scope of PROMs within this field and their validity by using novel and established PRO assessment frameworks (Chapter 2).
- Develop and implement a bespoke validation framework to demonstrate the psychometric properties of the SPUR model in patients diagnosed with T2D (Chapter 3).
- Demonstrate the cross-cultural validity and psychometric properties of the SPUR model in a new patient population of people diagnosed with COPD (Chapter 4).
- Evaluate and compare SPUR with other PROMs of MA as predictors of real-world health outcomes for patients living with T2D including general and early hospital readmissions (Chapter 5).

6.2 Key Findings

Chapter 2 provided clear quantitative evidence to demonstrate that a significant proportion of studies failed to present the minimum threshold of one validity criterion for PROMs included within their reports. When evaluated at a SR level, this translated in almost two-thirds of reviews reporting PROMs without evidence of validity. Churruca *et al*[192] report similar findings in their review. The authors highlighted that while PROM literature continues to expand, inappropriate selection of PROMs that deviate from their original purpose without adequate evidence of validity is a growing challenge. Yet despite concerns around validity, Fleischmann and Vaughan[437] describe the routine use of PROMs as "paramount" to the future delivery of a patient-centred clinical model of care. The adaptive methodology and real-world application of SPUR embedded within this thesis demonstrate the opportunity for compromise between overly cautious validation and rapid clinical uptake without due diligence, with a hope that this approach can be utilised by future researchers/clinicians.

Chapter 2 also identified a significant correlation between journals with a lower impact factor and an increase in studies reporting PROMs without adequate evidence of validity. This finding raises questions about the standardisation of the review process for this area of research, as well as methods for reporting PROMs within the literature.[438-440] The results of this Chapter demonstrate a potentially unmet educational need for critical analysis among future generations of HCPs and researchers that will undoubtedly embed a growing number of PROMs within their clinical practice or studies. Similarly, Brunelli *et al*[441] have identified that while HCP attitudes toward PROMs are positive, major barriers to implementation are training and the availability of resources.

As the name suggests, the revised SPUR-27 model contained 27 items, yet despite removal of items, it reported greater estimates of internal consistency and known group validity related

to socio-demographic factors including age, income, BMI, and the number of prescribed antiglycaemic agents. These findings echoed associations between adherence and socio-clinical factors in T2D reported across several other reviews and studies.[442-445] However, as described by Pareja-Martinez *et al*[446] in their review of validity criteria reporting for PROMs of MA, known-group validity is poorly assessed as part of psychometric analyses, limiting the overall assessment of validity for PROMs. Access to socio-clinical data, even if self-reported, is often straightforward within both research and clinical settings. This thesis therefore emphasises the potential benefit of broader psychometric analyses, including known-group validity, to improve the outcomes of future PROM research. Moreover, it outlined that item redundancy, artificially exaggerated internal consistency, and poor description of clinical phenomena are critiques associated with unidimensional measures.[447,448] While SPUR-27 does evaluate the overall trait of MA as evidenced by the study and the comparison provided with objective measures e.g., HbA_{1c}, neither the items nor constructs are homogenous in their assessment of patient behaviour. Nevertheless, this approach lends itself to the development of a more comprehensive patient profile, and as a result, improved clinical utility of the model.[447]

Building on the theme of an expanded methodology, Chapter 4 utilised an ROC-AUC analysis to identify a new cut-off score, which could distinguish between adherent and non-adherent patients. This provided more consistent results for specificity and sensitivity when compared to both the original SPUR-27 scoring methodology and the MPR tool, which were both highly specific but poorly sensitive. While CCA is typically described in the context of language or cultural adaptation,[449-451] Chapter 2 provided a comprehensive evaluation and commentary on the broad lack of CCA for PROMs relevant to this research, and the resulting impact on validity. Chapter 4 sought to address this, however, despite the success of the

study, the model was not completely congruent with the one described for the T2D cohort. This finding emphasises the importance of iterative testing for validity over time as described by Parker *et al*.[318] At the time of writing, this recommendation has yet to be integrated within any consensus guideline for PROM development or evaluation e.g., COSMIN.

To the author's knowledge, VMATT2 Readmission is the first study to provide evidence and describe the relationship between a multidimensional model of MA and readmission risk. While the relationship has been described previously in patients with T2D, studies have implemented unidimensional measures of MA, including MMAS.[452] The level of MA is therefore characterised using a binary model, adherent *vs* non-adherent, however MMAS in this case fails to describe the behavioural determinants linked to non-adherence and may lack clinical utility, as highlighted by Carrozzino *et al*.[447] SPUR-27 therefore reflects a shift and future approach to model development comprising both real-world applications and a greater capacity for efficacy in the context of clinical decision making by moving beyond a binary outcome. Instead, SPUR-27, as a multi-dimensional model, offers a contextualised profile of patient behaviour that not only describe the level of adherence, but perhaps more critically, the *why* behind this behaviour. The thesis author postulates that in answering the *why*, future researchers and clinicians may also begin to address the unmet need for clinically effective MA interventions with models such as SPUR-27.

6.3 Limitations

While suitable sample sizes were met for the VMATT2 and VMATC studies as part of this thesis, recruitment was primarily conducted in Southwest London, particularly in the Kingston Upon Thames region where the main hospital for this study was based. The local population are disproportionately affluent when compared to other regions in London, but also nationally. Deprivation can have a significant role in determining health behaviours,

hence exploring the potential impact of MA and related-behaviour among less affluent populations may produce different results for the SPUR-27 model. Moreover, Kingston is neither fully reflective of national or the Greater London demographic distribution in terms of ethnicity, hence attitudes and experiences of other ethnicities may have not been adequately captured within this study and thus warrants further investigation.

An exception to the suitable sample size was the VMATT2 Readmission study. While the study produced strong findings in both the predictive capacity and calibration of the models, much larger data sets are required to provide confidence around the validity of SPUR-27 as a suitable predictor of admission and early readmission that could be implemented within clinical practice.

Although no true gold-standard PROM for MA exists, the scoping review conducted in Chapter 3 identified the most suitable comparators to include in the validation study. However, licenses were unobtainable for several of the initial models selected as part of the review process and alternatives had to be chosen to explore the psychometric properties of SPUR-27. One might argue that adoption of more widely recognised PROMs, such as the MMAS, would have provided stronger evidence of the value for a multidimensional model such as SPUR-27. Despite this, VMATT2 and VMATC produced significant results across a broad range of psychometric properties, which also included outcomes measures used in routine clinical practice e.g., HbA_{1c}, which suggests the results are reliable and support the validity of SPUR-27.

This thesis focused on EFA as a predominant methodology for providing early evidence of psychometric properties for SPUR-27. CFA is a more powerful statistical technique than EFA given that it can explore whether observed data fit with the initial hypothesis for a model. A core hypothesis underlying the development and delivery of this thesis centres on

the superiority of multidimensional models, specifically in relation to complex behaviours such as MA. Without CFA, this thesis can only cautiously speculate on whether this hypothesis has been sufficiently addressed. However, one important strength of this thesis was the inclusion of PCFA that produced significant results in the absence of large sets of previous data from which to support the full implementation of CFA.

6.3.1 Reflections on the Impact of the Covid-19 Pandemic

The Covid-19 pandemic has had several impacts on the studies conducted during the completion of the thesis. Most notably, the first lockdown in March 2020 caused significant disruption to the delivery of the VMATT2 study. At the time, all face-to-face research activities were paused by Kingston University and Kingston Hospital. Moreover, patients were advised to stop attending community pharmacies with a move toward postal delivery of medicines where possible that directly impacted recruited from the community arm of the study. While some data were collected, even upon the end of the lockdown and approval to reengage in research, significant shifts in patient behaviour had occurred that may have affected the study results as discussed in the previous Chapters. For example, patients had their medicine delivered. This was likely to create abnormally high reports for MPR calculations. Moreover, patients were less likely to attend a HbA_{1c} check-up and routine collection of lung function tests among other clinical markers of COPD severity and prognosis were essentially stopped. Test-retest reliability procedures were also cancelled due to the unjustifiable risk of asking patients to reattend a clinical setting just to recomplete the research study documentation. While it may have been possible to call patients and complete this over the phone, this would have been incredibly challenging due to the length of the questionnaire and may have inadvertently affected the “patient-reported” aspect of the methodology. The methods were intended to provide patients with the opportunity to

complete the SPUR-27 tool in their own time. However, some patients were aided by the thesis author in completing the tool. This may have contributed to unwanted bias in the results through concepts such as social desirability.

Covid-19 precautions was included in the plan for VMATC study recruitment retrospectively by updating the methods to include the recommendations by Kingston Hospital for Covid-19 appropriate research on-site. This included the use of Personal Protective Equipment to ensure that patients were still able to take part, as well as disinfecting study materials where possible. While this approach supported on-site recruitment, public health measures for the public at the time of the study resulted in patients and HCPs seeking to avoid hospital admissions where reasonable, hence a lower than typical sample of patients living with COPD were seen due to a shortened period of recruitment.

Covid-19 also played a clear role in affecting the way patients accessed care during the pandemic. This was a specific consideration for VMATT2 Readmission whereby a Covid-19 diagnosis prior to the study was likely to reduce the risk of hospital admission. The thesis author surmised that this may have been due to increased access to care that inadvertently may have reduced the risk of admission in the future. Moreover, literature included in Chapter 5 describes how specific pharmacological agents, such as GLP-1R agonists, pioglitazone, and DPP-4 inhibitors, may have played a role in outcomes for patients diagnosed with T2D that might have had a confounding impact on health outcomes for patients includes in the VMATT2 Readmission study. [435] These findings raise an important question about the long-term impact of Covid-19 on patient behaviour, not only in relation to MA, but more generally in accessing care, self-management of chronic conditions, as well as communication with HCPs that may have a sizeable impact on results for new as well as previously validated PROMs.

6.4 Knowledge Advancement

This thesis has taken several important preliminary steps in demonstrating the psychometric properties of a multidimensional model of MA in patients diagnosed with chronic conditions. Preliminary results support the strong predictive capability of SPUR-27 in real-world health outcome assessments, such as hospital admission and early readmission, even when compared with previously validated PROMs. Moreover, research included within this thesis has identified novel results in areas such as bibliometric reliability, the validity and reporting of PROMs in the literature, and insights into the impacts of Covid-19 on research as well as clinical practice and patient behaviour during the pandemic.

The thesis supports the growing trend within the field of PROM research that 'validity' is not a static concept. In fact, the disparities in results between the VMATT2 and VMATC studies demonstrate the challenges associated with CCA and the need to avoid assumptions around how well a PROM may or may not perform in other patient populations, irrespective of how similar they may appear to be at face-value. Furthermore, it is also clear that early descriptions of this research space as 'qualitatively complex' are certainly true. While methodologies such as COSMIN and the FDA PRO guidance exist, their adoption is neither universal nor feasible or appropriate. Bespoke methodologies for PROM research, such as those implemented periodically throughout this thesis, may improve the reporting and validity of PROMs by striking a balance between extensive and complex analyses and the experience or time of clinicians and researchers who may be looking to rapidly adopt PROMs in practice with a view to improve patient care.

Innovations that can address the growing burden of chronic disease, multimorbidity, and MA are essential to improve patient outcomes and experience as well as address the huge associated health economic burden. The findings presented in this thesis provide evidence

that PROMs, such as SPUR-27, can be used to reliably explore complex behaviours in patients living with chronic conditions, identify differences in MA, and perhaps most importantly identify and monitor individualised risks and changes in health outcomes related to MA that could be used to inform clinical decision making and improve the quality of care patients receive in different settings, such as community pharmacies and hospitals. By centring individual patient experience within a model of care using tools such as SPUR-27, the hope is that patients and clinicians can feel increasingly empowered to manage MA.

6.5 Recommendations & Practice Implications

When looking to develop a framework that can provide evidence of validation for a psychometric model such as SPUR-27, the following points should be considered:

- Previous evidence of validity for models should not be assumed. Researchers should conduct their own assessment of PROM reporting while adopting methods previously used to assess validity when seeking suitable PROMs for inclusion in research studies or reviews. The thesis provides a simplified 3-step reporting framework, which may be adopted in future PROM guidelines that can help to address challenges associated with more complex initiatives e.g., COSMIN.
- An iterative and continuous approach to the evaluation of PROMs should be followed such that validity is not assumed after a single provision of psychometric properties for a model. Similarly to the reporting framework, future PROM guidance should reflect the variable nature of validity. This is particularly true in regard to CCA, and importantly in the context of sociological phenomena, such as Covid-19, that have the potential to bias results at a population level e.g., national changes in HbA_{1c} reporting.
- The use of frameworks such as COSMIN or those developed and described in this thesis can support the standardisation of research or reporting of PROMs and related

research. Policy and/or guidance related to the use of PROMs within research should include such frameworks within their scope of assessment. For example, PROMs are commonly used within RCTs, yet the NHS/HRA ethical review process does not critically analyse the appropriateness or evidence for PROMs included within submitted statistical analysis plans for proposed studies. This also identifies a potential unmet educational need as well as a potential role for health psychologists and other professionals with experience in PROMs as part of the NHS research ethics review process within the UK.

- Multidimensional PROMs may have specific benefits in comprehensive assessments of patient behaviour and related risks; however, it is also important to consider the adoption and clinical relevance of a model e.g., a PROM with >100 items may provide a more detailed patient profile but is less likely to be adopted in clinical practice.
- The value of PROMs can extend beyond isolated assessments of specific health outcomes. Where feasible, PROMs should be integrated and assessed as part of predictive modelling to support the identification and development of potential interventions in real-world settings.

6.6 Dissemination, Impact, and Future Work

Through the course of this thesis, four research articles, which includes one SR, have been published in quartile one peer reviewed journals. In addition, three corresponding articles have been published following their presentation at the national Health Services Research and Pharmacy Practice conferences in 2021 and 2023. At the time of writing, one additional conference acceptance has been received as outlined below. The results of this thesis were

also disseminated through other channels to improve the reach and potential impact, including:

- The Kingston Hospital intranet and research portal, which reported successful completion of three separate studies conducted onsite (VMATT2, VMATC, and VMATT2Readmission).
- Via local Kingston University media channels (Instagram, Linkedin, and Kingston website) to reflect both the results of the studies but also highlight the benefits of commercial-academic relationships in the context of research. Moreover, the results were similarly disseminated by the research partner, Observia, through their UK media channels as well as their French and international communications list that led to seven media outlets reporting on the studied across the UK and France.

The thesis author is currently in discussions with Observia, the PhD funder, to outline future work that can follow this thesis.

This thesis has developed a bespoke validation methodology in line with other international assessment frameworks such as COSMIN to deliver two validation and one observational cohort studies to explore the psychometric properties of SPUR-27 and its association with real-world health outcomes. Future work will include:

- Confirming the cross-cultural validity of the SPUR model with ethnic minorities and less affluent populations.
- Implementing a feasibility study to assess the acceptability of SPUR as a predictive behavioural model for MA discussions/interventions by pharmacists in community, hospital, and primary care settings.

- Conducting an international meta-analysis of the data collected from the UK, French, US, and Chinese studies for SPUR with patients diagnosed with hypertension, breast cancer, multiple sclerosis, T2D, and COPD.
- Developing an interventional RCT to explore the impact of interventions informed by data from SPUR-27 in a large cohort of patients diagnosed with chronic conditions in secondary care.
- Exploring the validity of the SPUR model in a preventative health model for a cohort of patients taking Pre-Exposure Prophylaxis (PrEP) to prevent the transmission of HIV.

6.7 Personal Reflections

Through completing a PhD, one might expect tangible benefits to include improvements in research skills, writing, and the ability to communicate scientific results. This is certainly the case for me; however one unexpected benefit was also a considerable change in my personal professional practice as a pharmacist. Training for pharmacists, both at an undergraduate and post-qualification level, is underpinned by the notion that the most effective way to provide care is through a patient-centred approach. Yet, when faced with the day-to-day pressures of clinical practice it can become increasingly easy to rely upon the protocolisation of care with the use of guidelines, standard-operating procedures, and other frameworks that outline a stepwise approach to medicine.

It is undeniable that evidenced-based medicine plays a critical role in keeping patients safe, reducing risk, and optimising the care they receive. Yet our focus on *evidence* can sometimes blind us to something that is poignantly *evident* - lots of patients are not taking their medicines. While conducting adherence-based research as part of this thesis, I have experienced a reframing in my evaluation of patients and their relationships with medicines.

This goes beyond a simple binary assessment of whether an individual can be considered "adherent", rather my assessment of patients has grown into something more holistic. Exploring social, psychological, environmental, and even political drivers of behaviour has become embedded into my standard engagement with patients. In doing so, not only have I developed stronger relationships with patients, but I have gained a new lens through which to understand a critical question identified in this thesis – *why are patients not taking their medicines?*

As the SPUR model has continued to evolve throughout this thesis, so have my reflections on the role of the pharmacist. The thesis has taught me that we can always play an important role in supporting the safe and effective use of medicines, but more critically, it has helped me recognise the true value of patient-centred care – establishing relationships, commonality, and that a conscious awareness of patients beyond their drug history and comorbidities has the potential to play a more pivotal role in their health than any medical intervention. Therefore, I can surmise that this PhD has not only helped me to develop as a researcher, but also as a clinician.

In summary, the PhD, particularly with the unexpected appearance of Covid-19, has at times felt like an unending marathon of obstacles and challenges. However, the beauty of hindsight is the ability to reflect on hardship and recognise the inherent value in overcoming the hurdles put before you. I can walk away feeling accomplished in the fact that I have contributed to novel research, supported organisational relationships (Kingston University & Observia), and developed professionally as an academic throughout my PhD journey, which I'm confident has had a positive effect on me personally, and I hope will continue to impact patients, colleagues, and students that I continue to work with in the future.

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Appendix A: Original SPUR-45 Questionnaire

SPUR Questionnaire *– Please choose the response that you feel best suits your personal situation. There are no right or wrong answers to any question.*

1. My diabetes affects my relationships with those I care about.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

I strongly disagree — I strongly agree

2. My diabetes affects my social life.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

I strongly disagree — I strongly agree

3. I would be interested in knowing if others with diabetes follow their treatment plan.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

I strongly disagree — I strongly agree

4. I think that people with diabetes generally follow their doctors' prescription exactly.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

I strongly disagree — I strongly agree

5. The people in my life help me manage my diabetes.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

I strongly disagree — I strongly agree

6. Fighting for my health is my highest priority.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

I strongly disagree — I strongly agree

7. Precisely following doctors' recommendations is the best way for me to stay healthy.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

I strongly disagree — I strongly agree

8. I trust doctors' recommendations.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

I strongly disagree I strongly agree

9. It is essential that I follow my treatment plan.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
I strongly disagree I strongly agree

10. Sometimes my COPD seems unreal to me.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
I strongly disagree I strongly agree

11. I'm the kind of person who will follow their treatment plan exactly.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
I strongly disagree I strongly agree

12. I will have to take a treatment for my diabetes for the rest of my life.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
I strongly disagree I strongly agree

13. I live in the moment.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
I strongly disagree I strongly agree

14. If my doctor recommends that I do something, I do it.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
I strongly disagree I strongly agree

15. Sometimes doctors prescribe treatment you don't really need.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
I strongly disagree I strongly agree

16. Sometimes I don't follow my treatment plan exactly.

☐ ☐ ☐ ☐ ☐

1	2	3	4	5
I strongly disagree				I strongly agree

17. I find it easy to get my treatment for my diabetes.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

18. I can easily pay for my treatment.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

19. I am able to follow my treatment plan.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

20. Too many doctors don't listen to what patients tell them.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

21. My diabetes has led to financial problems.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

22. I find it easy to follow my treatment plan when I am not at home.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

23. I am satisfied with the level of information I have about my treatment.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

24. I find it easy to manage the different medications I take.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

25. I find it easy to take my medication for my diabetes.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

26. I am worried about the side effects of some medications.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

27. I believe I can stop my treatment for my diabetes when I feel better.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

28. I am worried about taking medications.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

29. My diabetes should be taken seriously.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

30. I am able to exercise despite my diabetes.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

31. My treatment affects my sex life.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

32. I am satisfied with the level of information I have about my diabetes.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

33. I completely understand my diabetes.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

34. I don't like taking medications.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

35. Medications for my diabetes don't do anything for me.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

36. My treatment helps my diabetes.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

37. There is no point in taking medications for my diabetes.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

38. What I do impacts my diabetes.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

39. My diabetes is likely to get worse if I don’t follow my treatment plan.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

40. I feel worse if I don't follow my treatment plan.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

41. Medications are more expensive than they should be.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

42. My diabetes keeps me from doing things I want to do.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

43. Following my diabetes treatment plan lets me do the things I want to do.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

44. Non-traditional treatments could replace some of my medications.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

45. I have found ways to deal with my diabetes.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

Appendix B: Comparator PROMs (BeMQ, DTSQ, MARS)

MARS Questionnaire *- We are interested in your experiences taking medications. There is no right or wrong answer. Please answer each question based on your personal experience with your diabetes medication.*

1. **Do you ever forget to take your diabetes medication?**

Yes ☐ **No** ☐

2. **Are you careless at times at taking medication for your diabetes?**

Yes ☐ **No** ☐

3. **When you feel better do you sometimes stop taking your diabetes medication?**

Yes ☐ **No** ☐

4. **Sometimes if you feel worse when you take the diabetes medication do you stop taking it?**

Yes ☐ **No** ☐

5. **I take my diabetes medication only when I am sick**

Yes ☐ **No** ☐

6. **It is unnatural for my mind and body to be controlled by diabetes medication**

Yes ☐ **No** ☐

7. **My thoughts are clearer on diabetes medication**

Yes ☐ **No** ☐

8. **By staying on diabetes medication, I can prevent getting sick**

Yes ☐ **No** ☐

9. **I feel weird, like a zombie, on diabetes medication**

Yes ☐ **No** ☐

10. **Diabetes medication makes me feel tired and sluggish**

Yes ☐ **No** ☐

BMQ Questionnaire *- We would like to ask you about your personal views about medicines prescribed for your diabetes. Please indicate the extent to which you agree or disagree with each statement. There are no right or wrong answers. We are only interested in your personal views.*

1. My health at present depends on my diabetes medicines

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

2. Having to take diabetes medication worries me

☐	☐	☐	☐	☐

1	2	3	4	5
I strongly disagree				I strongly agree

3. My life would be impossible without my diabetes medication

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

4. Without my diabetes medication I would be very ill

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

5. I sometimes worry about the long term effects of my diabetes medication

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

6. My diabetes medication is mystery to me

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

7. My health in the future will depend on my diabetes medication

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

8. My diabetes medication disrupts my life

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

9. I sometimes worry about becoming too dependent on my diabetes medication

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

10. My diabetes medication protects me from becoming worse.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

BMQ-General

- We would like to ask you about your personal views about medicines in general.
- These are statements other people have made about medicines in general.
- Please indicate the extent to which you agree or disagree with them by ticking the appropriate box.
- There are no right or wrong answers.
- Please only tick one box per question.

11. Doctors use too many medicines

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

12. People who take medicines should stop their treatment for a while every now and again.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

13. Most medicines are addictive.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

14. Natural remedies are safer than medicines

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

15. Medicines do more harm than good.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

16. All medicines are poisons

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

17. Doctors place too much trust on medicines

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

18. If doctors had more time with patients they would prescribe fewer medicines.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

DTSQ-s Questionnaire *- The following questions are concerned with the treatment of your diabetes (including insulin, tablets, and/or diet) and your experience over the past few weeks.*

1. How satisfied are you with your current treatment?

☐	☐	☐	☐	☐	☐	☐
0	**1**	**2**	**3**	**4**	**5**	**6**
Very dissatisfied						Very satisfied

2. How often have you felt that your blood sugars have been unacceptably high recently?

☐	☐	☐	☐	☐	☐	☐
0	**1**	**2**	**3**	**4**	**5**	**6**
None of the time						Most of the time

3. How often have you felt that your blood sugars have been unacceptably low recently?

☐	☐	☐	☐	☐	☐	☐
0	**1**	**2**	**3**	**4**	**5**	**6**
None of the time						Most of the time

4. How convenient have you been finding your treatment recently?

☐	☐	☐	☐	☐	☐	☐
0	**1**	**2**	**3**	**4**	**5**	**6**
Very inconvenient						Very convenient

5. How flexible have you been finding your treatment to be recently?

☐	☐	☐	☐	☐	☐	☐
0	**1**	**2**	**3**	**4**	**5**	**6**
Very inflexible						Very flexible

6. How satisfied are you with your understanding of your diabetes?

☐	☐	☐	☐	☐	☐	☐
0	**1**	**2**	**3**	**4**	**5**	**6**
Very dissatisfied						Very satisfied

7. Would you recommend this form of treatment to someone else with your kind of diabetes?

☐	☐	☐	☐	☐	☐	☐
0	**1**	**2**	**3**	**4**	**5**	**6**

No, definitely not Yes, definitely

8. How satisfied would you be to continue with your present form of treatment?

☐ ☐ ☐ ☐ ☐ ☐ ☐

0 1 2 3 4 5 6

Very dissatisfied Very satisfied

Appendix C: Pilot Patient Consent Form

WRITTEN CONSENT TO PARTICIPATE IN A RESEARCH STUDY (for patients)

Statement by participant

- I confirm that I have read and understood the information sheet/letter of invitation for this study. I have been informed of the purpose, risks, and benefits of taking part.

Validating an adherence measuring tool and evaluating its feasibility as a profiling tool for personalised medicines optimisation interventions by pharmacists – Pilot Study

- I understand what my involvement will entail and any questions have been answered to my satisfaction.
- I understand that my participation is entirely voluntary, and that I can withdraw at any time without prejudice.
- I understand that all information obtained will be confidential.
- I agree that research data gathered for the study may be published provided that I cannot be identified as a subject.
- Contact information has been provided should I (a) wish to seek further information from the investigator at any time for purposes of clarification (b) wish to make a complaint.

Participant's Signature----------

Date ----------

Statement by investigator

- I have explained this project and the implications of participation in it to this participant without bias and I believe that the consent is informed and that he/she understands the implications of participation.

Name of investigator Joshua Sterling Wells

Signature of investigator ----------

Date ----------

Appendix D: Pilot Patient Participant Information Sheet

Patient Information Sheet

Validating an adherence measuring tool and evaluating its feasibility as a profiling

tool for personalised medicines optimisation interventions by pharmacists – Pilot Study

[11/04/2019]

You are being invited to take part in a PhD pilot project. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information sheet carefully before deciding whether or not to participate. The project consists of completing a prototype questionnaire that is used to assess how certain behaviour can impact the ability to take medicines for a medical condition.

What is the purpose of the study?

The primary aim of this study is to determine what factors related to patient behaviour may affect their ability to take their medicines.

Why have I been chosen?

You represent an individual that falls into a key stakeholder category identified at the start of the project as a target audience for the study. More specifically, you are an individual that takes regular medication for Type 2 Diabetes.

Do I have to take part?

No. This research study is done purely on a voluntary basis. If you choose to take part after reading this information sheet, we will continue with the session. Before completing any activities, I will ask you to sign an informed consent. You are free to withdraw from this study at any point without disadvantage and without having to provide a reason. Any data collected prior to withdrawal will be erased on confirmation you no longer wish to proceed with the study.

What will happen to me if I take part?

You will be asked to complete a questionnaire that has been developed by the research team. The questionnaire includes statements and you will be asked to what degree to you agree or disagree, ticking the box that applies most to you. These questions will be related to your thoughts on your type 2 diabetes, as well as your thoughts on taking medicines among other related topics. Additionally, you will be asked to highlight questions e.g. you may not want to answer these questions or find them challenging. You do not have to complete a question if you do not want to. However, if you highlight a question, we will ask for your feedback on that specific question. Following completion of the questionnaire, you will be asked to complete some additional questions with your feedback. Additionally, you will be asked about your most recent HbA1C result. If you know your HbA1c result, but do not want to provide an answer, you are under no obligation to do so and please skip this question. Finally, you will be asked to complete a few questions related to your demographic information such as your age range. Throughout the process the lead researcher will be available to answer any questions you may have.

What are the possible benefits of taking part?

Although there is no actual medical benefit from the study, you will be providing input to a university PhD research project as well as developing research in the area of medication adherence. Your contribution to this project will help shape the future of the research in terms of the direction for moving forwards e.g. potential applications for real-time assessment of patient adherence in chronic conditions to help develop tools to improve patient medication taking behaviours and hopefully their quality of life.

What are the possible disadvantages and risks of taking part?

There are no perceived disadvantages or risks. Your time is very valuable for this project and therefore if you do decide to take part this may take up to 15-20 minutes of your time.

What happens when the research study ends?

You will be under no obligation to volunteer again. Contact details for myself plus project supervisor are included at the end of this information sheet should you wish to ***discuss the findings***.

Will my taking part be kept confidential?

All information collected during the course of the study will be kept strictly confidential and in secure storage. Responses will be anonymised before analysis so that it will not be possible to identify you or any other participant. Only I and the project supervisor will have access to this dataset.

Any personal information collected will be immediately destroyed, except that required by the University research policy.

Who is organising and funding the study?

This study is part of my PhD project, within the School of Pharmacy, Faculty of Science, Engineering and Computing, at Kingston University. Observia, an e-health solution organisation based in France are the main sponsor for the project. None of the investigators stands to gain financially from this study.

What will happen to the results of the research study?

The results will be part of my thesis which will be made available in the Faculty of Science, Engineering and Computing Learning Resources Centre (library) at Kingston University for others to view. In addition, findings arising from this study may be presented at national and international conferences as well as published in scientific journals. It will not be possible to identify you or others from any such publications with results being aggregated for the whole group. In such cases where an interview is used, if you permit for the interview to be recorded and transcribed, participants will always be referred to by pseudonyms.

Please contact myself or my supervisor, Professor Reem Kayyali if you have any questions about this project. You are welcome to contact myself or Professor Kayyali on the emails detailed below should you require any further information or support following your participation in the study.

Who has reviewed the study?

The Kingston University Faculty of Science, Engineering and Computing Research Ethics Committee has reviewed and approved this study.

In addition, this project is being supervised by Professor Reem Kayyali and Philip Crilly

Contact for further information.
Further information may be obtained from:

Joshua Wells – k1213537@kingston.ac.uk

Reem Kayyali – r.kayyali@kingston.ac.uk

If you become concerned about any issue that may have been raised by you participating in this study, please contact myself or Professor Reem Kayyali

For any concerns relating to data protection please contact the university's Data Protection Officer i.e. dpo@kingston.ac.uk

Thank you for taking the time to read this information sheet.

Appendix E: Pilot Community Pharmacist Participant Information Sheet

Community Pharmacist Information Sheet

Validating an adherence measuring tool and evaluating its feasibility as a profiling

tool for personalised medicines optimisation interventions by pharmacists – Pilot Study

[22/10/18]

You are being invited to take part in a PhD pilot project. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information sheet carefully before deciding whether or not to participate. The project consists of reviewing a questionnaire used to assess medication adherence. You will be asked to review the pilot questionnaire as well as provide feedback using a Likert-scale questionnaire and any additional thoughts you may have. If you decide not to take part, there will be no disadvantage to you and I thank you for your time in considering my project. If after reading this information sheet, you are still unsure or uncertain about anything, then I am happy to answer any questions you may have. You should not sign the consent form until your queries have been resolved and you are happy to volunteer.

What is the purpose of the study?

The primary aim of this study is to determine what factors related to patient behaviour may affect their ability to take their medicines..

Why have I been chosen?

You represent an individual that falls into a key stakeholder category identified at the start of the project as a target audience for the study. More specifically, you are a community pharmacist that has regular contact with patients and therefore your feedback on the questionnaire would be valuable for this project.

Do I have to take part?

No. This research study is done purely on a voluntary basis. If you choose to take part after reading this information sheet, I will ask you to sign a consent form and we will proceed with the review of the questionnaire. You are free to withdraw from this study at any point without disadvantage and without having to provide a reason.

What will happen to me if I take part?

You will be asked to review a questionnaire developed by the research team. You will then be given an opportunity to interact with the questionnaire and you will be asked to provide feedback. You will be given the opportunity to ask questions and to confirm your consent prior to the review. Your feedback will provide us with information on how well the questionnaire works, and whether it is a suitable method to collect data on how patients take/don't take their medicines.

What are the possible benefits of taking part?

You will be providing input to a university PhD research project as well as developing research in the area of medication adherence. Your contribution to this project will help shape the future of the research in terms of the direction for moving forwards e.g. potential applications for real-time assessment of patient adherence in chronic conditions to help

develop tools to improve patient medication taking behaviours and hopefully their quality of life.

What are the possible disadvantages and risks of taking part?

There are no perceived disadvantages or risks. Your time is very valuable for this project and therefore if you do decide to take part this may take up to 15-20 minutes of your time.

What happens when the research study ends?

You will be under no obligation to volunteer again. Contact details for myself plus project supervisor are included at the end of this information sheet should you wish to ***discuss the findings***.

Will my taking part be kept confidential?

All information collected during the course of the study will be kept strictly confidential and in secure storage. Responses will be anonymised before analysis so that it will not be possible to identify you or any other participant. Only I and the project supervisor will have access to this dataset.

Any personal information collected will be immediately destroyed, except that required by the University research policy.

Who is organising and funding the study?

This study is part of my PhD project, within the School of Pharmacy, Faculty of Science, Engineering and Computing, at Kingston University. Observia, an e-health solution organisation based in France are the main sponsor for the project. None of the investigators stands to gain financially from this study.

What will happen to the results of the research study?

The results will be part of my thesis which will be made available in the Faculty of Science, Engineering and Computing Learning Resources Centre (library) at Kingston University for others to view. In addition, findings arising from this study may be presented at national and international conferences as well as published in scientific journals. It will not be possible to identify you or others from any such publications with results being aggregated for the whole group. In such cases where an interview is used, if you permit for the interview to be recorded and transcribed, participants will always be referred to by pseudonyms.

Please contact myself or my supervisor, Professor Reem Kayyali if you have any questions about this project.

Who has reviewed the study?

The Kingston University Faculty of Science, Engineering and Computing Research Ethics Committee has reviewed and approved this study.

In addition, this project is being supervised by Professor Reem Kayyali and Philip Crilly

Contact for further information.

Further information may be obtained from:

Joshua Wells – k1213537@kingston.ac.uk

Reem Kayyali – r.kayyali@kingston.ac.uk

If you become concerned about any issue that may have been raised by you participating in this study, please contact myself or Professor Reem Kayyali

For any concerns relating to data protection please contact the university's Data Protection Officer i.e. dpo@kingston.ac.uk

Thank you for taking the time to read this information sheet.

Appendix F: Pilot Community Pharmacist Consent Form

WRITTEN CONSENT TO PARTICIPATE IN A RESEARCH STUDY (for community pharmacists)

Statement by participant

- I confirm that I have read and understood the information sheet/letter of invitation for this study. I have been informed of the purpose, risks, and benefits of taking part.

Validating an adherence measuring tool and evaluating its feasibility as a profiling tool for personalised medicines optimisation interventions by pharmacists – Pilot Study

- I understand what my involvement will entail and any questions have been answered to my satisfaction.
- I understand that my participation is entirely voluntary, and that I can withdraw at any time without prejudice.
- I understand that all information obtained will be confidential.
- I agree that research data gathered for the study may be published provided that I cannot be identified as a subject.
- Contact information has been provided should I (a) wish to seek further information from the investigator at any time for purposes of clarification (b) wish to make a complaint.
- I agree to take part in review session where my feedback will be recorded and collected for the study.

Participant's Signature----------

Date ----------

Statement by investigator

- I have explained this project and the implications of participation in it to this participant without bias and I believe that the consent is informed and that he/she understands the implications of participation.

Name of Investigator Joshua Sterling Wells

Signature of investigator ----------

Date ----------

Appendix G: Pilot Medicines Optimisation Expert Participant Information Sheet

Expert Information Sheet

Validating an adherence measuring tool and evaluating its feasibility as a profiling

tool for personalised medicines optimisation interventions by pharmacists – Pilot Study

[22/10/18]

You are being invited to take part in a PhD pilot project. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information sheet carefully before deciding whether or not to participate. The project consists of reviewing a questionnaire used to assess medication adherence. You will be asked to review the pilot questionnaire as well as provide feedback using a Likert-scale questionnaire and any additional thoughts you may have. If you decide not to take part, there will be no disadvantage to you and I thank you for your time in considering my project. If after reading this information sheet, you are still unsure or uncertain about anything, then I am happy to answer any questions you may have. You should not sign the consent form until your queries have been resolved and you are happy to volunteer.

What is the purpose of the study?

The primary aim of this study is to determine what factors related to patient behaviour may affect their ability to take their medicines.

Why have I been chosen?

You represent an individual that falls into a key stakeholder category identified at the start of the project as a target audience for the study. More specifically, you are a healthcare professional with specialist experience/knowledge in the area of medication adherence that has regular contact with patients and therefore your feedback on the questionnaire would be valuable for this project.

Do I have to take part?

No. This research study is done purely on a voluntary basis. If you choose to take part after reading this information sheet, I will ask you to sign a consent form and we will proceed with the review of the questionnaire. You are free to withdraw from this study at any point without disadvantage and without having to provide a reason.

What will happen to me if I take part?

You will be asked to review a questionnaire developed by the research team. You will then be given an opportunity to interact with the questionnaire and you will be asked to provide feedback. You will be given the opportunity to ask questions and to confirm your consent prior to the review. Your feedback will provide us with information on how well the questionnaire works, and whether it is a suitable method to collect data on how patients take/don't take their medicines.

What are the possible benefits of taking part?

You will be providing input to a university PhD research project as well as developing research in the area of medication adherence. Your contribution to this project will help

shape the future of the research in terms of the direction for moving forwards e.g. potential applications for real-time assessment of patient adherence in chronic conditions to help develop tools to improve patient medication taking behaviours and hopefully their quality of life.

What are the possible disadvantages and risks of taking part?

There are no perceived disadvantages or risks. Your time is very valuable for this project and therefore if you do decide to take part this may take up to 15-20 minutes of your time.

What happens when the research study ends?

You will be under no obligation to volunteer again. Contact details for myself plus project supervisor are included at the end of this information sheet should you wish to ***discuss the findings***.

Will my taking part be kept confidential?

All information collected during the course of the study will be kept strictly confidential and in secure storage. Responses will be anonymised before analysis so that it will not be possible to identify you or any other participant. Only I and the project supervisor will have access to this dataset.

Any personal information collected will be immediately destroyed, except that required by the University research policy.

The interviews will be recorded however once transcribed the recording will be deleted and the data stored on a secured password protected server.

Who is organising and funding the study?

This study is part of my PhD project, within the School of Pharmacy, Faculty of Science, Engineering and Computing, at Kingston University. Observia, an e-health solution organisation based in France are the main sponsor for the project. None of the investigators stands to gain financially from this study.

What will happen to the results of the research study?

The results will be part of my thesis which will be made available in the Faculty of Science, Engineering and Computing Learning Resources Centre (library) at Kingston University for others to view. In addition, findings arising from this study may be presented at national and international conferences as well as published in scientific journals. It will not be possible to identify you or others from any such publications with results being aggregated for the whole group. In such cases where an interview is used, if you permit for the interview to be recorded and transcribed, participants will always be referred to by pseudonyms.

Please contact myself or my supervisor, Professor Reem Kayyali if you have any questions about this project.

Who has reviewed the study?

The Kingston University Faculty of Science, Engineering and Computing Research Ethics Committee has reviewed and approved this study.

In addition, this project is being supervised by Professor Reem Kayyali and Philip Crilly

Contact for further information.
Further information may be obtained from:

Joshua Wells – k1213537@kingston.ac.uk

Reem Kayyali – r.kayyali@kingston.ac.uk

If you become concerned about any issue that may have been raised by you participating in this study, please contact myself or Professor Reem Kayyali

For any concerns relating to data protection please contact the university's Data Protection Officer i.e. dpo@kingston.ac.uk

Thank you for taking the time to read this information sheet.

Appendix H: Pilot Medicines Optimisation Expert Consent Form

WRITTEN CONSENT TO PARTICIPATE IN A RESEARCH STUDY (for expert participants)

Statement by participant

- I confirm that I have read and understood the information sheet/letter of invitation for this study. I have been informed of the purpose, risks, and benefits of taking part.

Validating an adherence measuring tool and evaluating its feasibility as a profiling tool for personalised medicines optimisation interventions by pharmacists – Pilot Study

- I understand what my involvement will entail and any questions have been answered to my satisfaction.
- I understand that my participation is entirely voluntary, and that I can withdraw at any time without prejudice.
- I understand that all information obtained will be confidential.
- I agree that research data gathered for the study may be published provided that I cannot be identified as a subject.
- Contact information has been provided should I (a) wish to seek further information from the investigator at any time for purposes of clarification (b) wish to make a complaint.
- I agree to take part in review session where my feedback will be recorded and collected for the study

Participant's Signature----------

Date ----------

Statement by investigator

- I have explained this project and the implications of participation in it to this participant without bias and I believe that the consent is informed and that he/she understands the implications of participation.

Name of Investigator Joshua Sterling Wells

Signature of investigator ----------

Date ----------

Appendix I: Pilot Patient Questionnaire

Dear participant,

Please read the following information carefully.

Please complete the following questionnaire by ticking the box for each statement that best applies to you. There is no time-limit for completion of the questionnaire, and the researcher is available to answer any additional questions you may have. There will be an opportunity to provide feedback after completion of the questionnaire. We estimate the questionnaire will take 10-15 minutes to complete.

Please use the colour marker provided to highlight any question that you have concerns with e.g. find it difficult to answer/are unable to provide an answer for. There is a small box at the end of the questionnaire where you can provide feedback on the questions you may have highlighted during completion.

Thank you for agreeing to take part in the session.

For each sentence, please tick the box that best applied to you.

1. **My diabetes affects my relationships with those I care about.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

2. **My diabetes affects my social life.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

3. **I would be interested in knowing if others with diabetes follow their treatment plan.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

4. **I think that people with diabetes generally follow their doctors' prescription exactly.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

5. **The people in my life help me manage my diabetes.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

6. **Fighting for my health is my highest priority.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

7. Precisely following doctors' recommendations is the best way for me to stay healthy.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

8. I trust doctors' recommendations.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

9. It is essential that I follow my treatment plan.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

10. Sometimes my COPD seems unreal to me.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

11. I'm the kind of person who will follow their treatment plan exactly.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

12. I will have to take a treatment for my diabetes for the rest of my life.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

13. I live in the moment.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

14. If my doctor recommends that I do something, I do it.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

15. Sometimes doctors prescribe treatment you don't really need.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

16. Sometimes I don't follow my treatment plan exactly.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

17. I find it easy to get my treatment for my diabetes.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

18. I can easily pay for my treatment.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

19. I am able to follow my treatment plan.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

20. Too many doctors don't listen to what patients tell them.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

21. My diabetes has led to financial problems.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

22. I find it easy to follow my treatment plan when I am not at home.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

23. I am satisfied with the level of information I have about my treatment.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

24. I find it easy to manage the different medications I take.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

25. I find it easy to take my medication for my diabetes.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

26. I am worried about the side effects of some medications.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

27. I believe I can stop my treatment for my diabetes when I feel better.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

28. I am worried about taking medications.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

29. My diabetes should be taken seriously.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

30. I am able to exercise despite my diabetes.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

31. My treatment affects my sex life.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

32. I am satisfied with the level of information I have about my diabetes.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

33. I completely understand my diabetes.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

34. I don't like taking medications.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

35. Medications for my diabetes don't do anything for me.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

36. My treatment helps my diabetes.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

37. There is no point in taking medications for my diabetes.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

38. What I do impacts my diabetes.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

39. My diabetes is likely to get worse if I don't follow my treatment plan.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

40. I feel worse if I don't follow my treatment plan.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

41. Medications are more expensive than they should be.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

42. My diabetes keeps me from doing things I want to do.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

43. Following my diabetes treatment plan lets me do the things I want to do.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

44. Non-traditional treatments could replace some of my medications.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

45. I have found ways to deal with my diabetes.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

1. The questions were easy to answer

Strongly Disagree 1	Disagree 2	Neither Agree Nor Disagree 3	Agree 4	Strongly Agree 5

2. I am happy with the length of the questionnaire

Strongly Disagree 1	Disagree 2	Neither Agree Nor Disagree 3	Agree 4	Strongly Agree 5

3. I would be happy to complete the questionnaire by myself

Strongly Disagree 1	Disagree 2	Neither Agree Nor Disagree 3	Agree 4	Strongly Agree 5

4. I believe this questionnaire could help improve my relationship with my medicines

Strongly Disagree 1	Disagree 2	Neither Agree Nor Disagree 3	Agree 4	Strongly Agree 5

5. The questions are relevant to my condition

Strongly Disagree 1	Disagree 2	Neither Agree Nor Disagree 3	Agree 4	Strongly Agree 5

6. When was your most recent HbA1c test?

7. If possible, please provide your most recent HbA1c result:

8. Any additional comments?

Demographic Questions

Age

25-29	
30-39	
40-49	
50-59	
60-69	
70-79	
80+	

Gender

Male	
Female	
Other	

Highest Level of Education

No formal education	
GCSE or Equivalent	
A-Level or Equivalent	
Bachelors Degree or Equivalent	
Post-graduate Degree or Equivalent	
Other (Please specify)	

Ethnicity

White	
Mixed / Multiple ethnic groups	
Asian / Asian British	
Black / African / Caribbean / Black British	
Other ethnic group (Please specify)	

Thank you for your time. Please return the completed questionnaire to the researcher who will be happy to answer any questions you may have.

Appendix J: Pilot Healthcare Professional Questionnaire

Dear participant,

Please read the following information carefully.

Please use the colour marker provided to highlight any question that you have concerns with e.g. poor wording/ perceived as challenging question for patient participants. There is a small box at the end of the questionnaire where you can provide feedback on the questions you may have highlighted. Additionally, there are a number of questions included to collect your feedback specifically about certain aspects about the questionnaire at the end of the document.

Thank you for agreeing to take part in the session.

For each sentence, please tick the box that best applied to you.

1. **My diabetes affects my relationships with those I care about.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

2. **My diabetes affects my social life.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

3. **I would be interested in knowing if others with diabetes follow their treatment plan.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

4. **I think that people with diabetes generally follow their doctors' prescription exactly.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

5. **The people in my life help me manage my diabetes.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

6. **Fighting for my health is my highest priority.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

7. **Precisely following doctors' recommendations is the best way for me to stay healthy.**

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

8. I trust doctors' recommendations.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

9. It is essential that I follow my treatment plan.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

10. Sometimes my COPD seems unreal to me.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

11. I'm the kind of person who will follow their treatment plan exactly.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

12. I will have to take a treatment for my diabetes for the rest of my life.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

13. I live in the moment.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

14. If my doctor recommends that I do something, I do it.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

15. Sometimes doctors prescribe treatment you don't really need.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

16. Sometimes I don't follow my treatment plan exactly.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

17. I find it easy to get my treatment for my diabetes.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

18. I can easily pay for my treatment.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

19. I am able to follow my treatment plan.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

20. Too many doctors don't listen to what patients tell them.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

21. My diabetes has led to financial problems.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

22. I find it easy to follow my treatment plan when I am not at home.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

23. I am satisfied with the level of information I have about my treatment.

☐	☐	☐	☐	☐
1	2	3	4	5

I strongly disagree I strongly agree

24. I find it easy to manage the different medications I take.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
I strongly disagree I strongly agree

25. I find it easy to take my medication for my diabetes.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
I strongly disagree I strongly agree

26. I am worried about the side effects of some medications.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
I strongly disagree I strongly agree

27. I believe I can stop my treatment for my diabetes when I feel better.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
I strongly disagree I strongly agree

28. I am worried about taking medications.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
I strongly disagree I strongly agree

29. My diabetes should be taken seriously.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
I strongly disagree I strongly agree

30. I am able to exercise despite my diabetes.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
I strongly disagree I strongly agree

31. My treatment affects my sex life.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

32. I am satisfied with the level of information I have about my diabetes.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

33. I completely understand my diabetes.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

34. I don't like taking medications.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

35. Medications for my diabetes don't do anything for me.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

36. My treatment helps my diabetes.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

37. There is no point in taking medications for my diabetes.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

38. What I do impacts my diabetes.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

39. My diabetes is likely to get worse if I don't follow my treatment plan.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

40. I feel worse if I don't follow my treatment plan.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

41. Medications are more expensive than they should be.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

42. My diabetes keeps me from doing things I want to do.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

43. Following my diabetes treatment plan lets me do the things I want to do.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

44. Non-traditional treatments could replace some of my medications.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

45. I have found ways to deal with my diabetes.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

Healthcare Professional Feedback Questionnaire

1. I feel the questions are patient appropriate

Strongly Disagree 1	Disagree 2	Neither Agree Nor Disagree 3	Agree 4	Strongly Agree 5

2. I feel the length of the questionnaire is appropriate

Strongly Disagree 1	Disagree 2	Neither Agree Nor Disagree 3	Agree 4	Strongly Agree 5

3. I would be happy to use this questionnaire to assess adherence for my patients

Strongly Disagree 1	Disagree 2	Neither Agree Nor Disagree 3	Agree 4	Strongly Agree 5

4. I believe this questionnaire can help improve patient relationships with their medicines

Strongly Disagree 1	Disagree 2	Neither Agree Nor Disagree 3	Agree 4	Strongly Agree 5

5. I believe the questionnaire would be easy for patients to complete by themselves

Strongly Disagree 1	Disagree 2	Neither Agree Nor Disagree 3	Agree 4	Strongly Agree 5

6. Any additional comments?

Demographic Questions

Age

25-29	
30-39	
40-49	
50-59	
60-69	
70-79	
80+	

Gender

Male	
Female	
Other	

Highest Level of Education

No formal education	
GCSE or Equivalent	
A-Level or Equivalent	
Bachelors Degree or Equivalent	
Post-graduate Degree or Equivalent	
Other (Please specify)	

Ethnicity

White	
Mixed / Multiple ethnic groups	
Asian / Asian British	
Black / African / Caribbean / Black British	
Other ethnic group (Please specify)	

Thank you for your time. Please return the completed questionnaire to the researcher who will be happy to answer any questions you may have.

Appendix K: VMATT2 Community Pharmacist Consent Form

WRITTEN CONSENT TO PARTICIPATE IN A RESEARCH STUDY (for pharmacists)

Statement by participant regarding study:

Validating an adherence measuring tool and evaluating its feasibility as a profiling tool for personalised medicines optimisation interventions by pharmacists

- I confirm that I have read and understood the information sheet/letter of invitation for this study. I have been informed of the purpose, risks, and benefits of taking part.
- I understand what my involvement will entail and any questions have been answered to my satisfaction.
- I understand that my participation is entirely voluntary, and that I can withdraw at any time without prejudice.
- I understand that all information obtained will be confidential and I am responsible for maintaining patient confidentiality
- I understand that I am responsible for collecting data from patients as part of the study, and will not share any identifiable information with the research team
- I agree for recruitment of patients within my pharmacy premises
- Contact information has been provided should I (a) wish to seek further information from the investigator at any time for purposes of clarification (b) wish to make a complaint.
- I agree that research data gathered for the study may be published provided that I cannot be identified as a subject.

Participant's Signature----------

Date ----------

Statement by investigator

- I have explained this project and the implications of participation in it to this participant without bias and I believe that the consent is informed and that he/she/they understands the implications of participation.

  Name of investigator (Joshua Wells): ----------

  Signature of investigator ----------

  Date ----------

Appendix L: VMATT2 Community Pharmacist Participant Information Sheet

Community Pharmacist Information Sheet

Validating an adherence measuring tool and evaluating its feasibility as a profiling tool for personalised medicines optimisation interventions by pharmacists

[11/04/2019]

You are being invited to take part in a PhD project. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information sheet carefully before deciding whether or not to participate. The project consists of delivering a questionnaire used to assess medication adherence to patients that use your pharmacy. If you decide not to take part, there will be no disadvantage to you and I thank you for your time in considering my project. If after reading this information sheet, you are still unsure or uncertain about anything, then I am happy to answer any questions you may have. You should not sign the consent form until your queries have been resolved and you are happy to volunteer.

What is the purpose of the study?

The primary aim of this study is to determine what factors related to patient behaviour may affect their ability to take their medicines.

Why have I been chosen?

You are a community pharmacist that supports patients with Type 2 Diabetes in the community through the provision of pharmacy services. Patients with Type 2 Diabetes are our target population for this study, therefore we are hoping to recruit healthcare professionals that have regular contact with this patient group.

Do I have to take part?

No. This research study is done purely on a voluntary basis. If you choose to take part after reading this information sheet, I will ask you to sign a consent form and we will proceed with the review of the questionnaire. You are free to withdraw from this study at any point without disadvantage and without having to provide a reason.

What will happen to me if I take part?

You will be asked to sign a consent form that confirms your agreement for recruitment of patients within your pharmacy. As part of the study, we will ask you to highlight eligible patients for the study that use your pharmacy services, as part of their normal clinical care. You will be asked to provide these patients with an information sheet about their involvement, as well as a consent form to confirm their participation. You will deliver the study questionnaire to the patient, who can complete this independently. However, we will also ask, with the patient's consent, for you to access their previous medication record (PMR). From the PMR, we will ask you to note the collection history of the patient's Type 2 Diabetes medicines over the previous 6 months. If patients choose to participate in a 6

month follow-up, you will be asked to secure their contact details (form attached to the patient questionnaire) and store these until the 6 month period where you will contact the patient to participate again in the study. At this point, you will be asked to re-consent the patient to access their PMR record for an additional 6 months of Diabetes medication collection data. Overall, you will be responsible for collecting and maintain the confidentiality of patient data.

What are the possible benefits of taking part?

You will be providing input to a university PhD research project as well as developing research in the area of medication adherence. Your contribution to this project will help shape the future of the research in terms of the direction for moving forwards e.g. potential applications for real-time assessment of patient adherence in chronic conditions to help develop tools to improve patient medication taking behaviours and hopefully their quality of life. You will be remunerated for your participation in the study, with funding of £7 for each survey completed, up to a maximum of £350 (50 patients recruited). This payment will be made irrespective of whether the patient consents to, or participates in the 6 month follow-up study.

What are the possible disadvantages and risks of taking part?

There are no perceived disadvantages or risks. Your time is very valuable for this project and therefore if you do decide to take part this may take up to 10 minutes of your time for each patient recruited including: providing the study materials, confirming consent and recording the patient's diabetes medication record.

What happens when the research study ends?

You will be under no obligation to volunteer again. Contact details for myself plus project supervisor are included at the end of this information sheet should you wish to ***discuss the findings***.

Will my taking part be kept confidential?

All information collected during the course of the study will be kept strictly confidential and in secure storage. Responses will be anonymised before analysis so that it will not be possible to identify you or any other participant. Only I and the project supervisor will have access to this dataset.

Any personal information collected will be immediately destroyed, except that required by the University research policy.

Who is organising and funding the study?

This study is part of my PhD project, within the School of Pharmacy, Faculty of Science, Engineering and Computing, at Kingston University. Observia, an e-health solution organisation based in France are the main sponsor for the project. None of the investigators stands to gain financially from this study.

What will happen to the results of the research study?

The results will be part of my thesis which will be made available in the Faculty of Science, Engineering and Computing Learning Resources Centre (library) at Kingston University for others to view. In addition, findings arising from this study may be presented at national and international conferences as well as published in scientific journals. It will not be possible to identify you or others from any such publications with results being aggregated for the whole group. In such cases where an interview is used, if you permit for the interview to be recorded and transcribed, participants will always be referred to by pseudonyms.

Please contact myself or my supervisor, Professor Reem Kayyali if you have any questions about this project.

Who has reviewed the study?

The Kingston University Faculty of Science, Engineering and Computing Research Ethics Committee has reviewed and approved this study.

In addition, this project is being supervised by Professor Reem Kayyali and Philip Crilly

Contact for further information.
Further information may be obtained from:

Joshua Wells – k1213537@kingston.ac.uk

Reem Kayyali – r.kayyali@kingston.ac.uk

If you become concerned about any issue that may have been raised by you participating in this study, please contact myself or Professor Reem Kayyali

For any concerns relating to data protection please contact the university's Data Protection Officer i.e. dpo@kingston.ac.uk

Thank you for taking the time to read this information sheet.

Appendix M: VMATT2 Patient Consent Form (Community)

WRITTEN CONSENT TO PARTICIPATE IN A RESEARCH STUDY (for patients)

Statement by participant regarding study:

Validating an adherence measuring tool and evaluating its feasibility as a profiling tool for personalised medicines optimisation interventions by pharmacists

- I confirm that I have read and understood the information sheet/letter of invitation for this study. I have been informed of the purpose, risks, and benefits of taking part.
- I understand what my involvement will entail and any questions have been answered to my satisfaction.
- I understand that my participation is entirely voluntary, and that I can withdraw at any time without prejudice.
- I understand that all information obtained will be confidential
- I understand that by voluntarily providing my contact details, I agree to be contacted regarding future participation in the study by my pharmacist and that I can withdraw from this at any point during the study
- I understand that only my pharmacist will have access to my contact information, and that all other information I provide will be anonymous
- I understand that by either participating, or not participating in this study, this will in no way impact the usual medical care I receive.
- I agree that research data gathered for the study may be published provided that I cannot be identified as a subject.
- Contact information has been provided should I (a) wish to seek further information from the investigator at any time for purposes of clarification (b) wish to make a complaint.
- I give permission for my pharmacist to review my diabetes medication collection information over the previous 6 months. I (agree / do not agree)* to be contacted again in 6 months to take part in this study again.

  *Delete as appropriate

Participant's Signature----------

Date ----------

Statement by investigator

- I have explained this project and the implications of participation in it to this participant without bias and I believe that the consent is informed and that he/she/they understands the implications of participation.

  Name of investigator (Community Pharmacist): ----------

  Signature of investigator ----------

  Date ----------

Appendix N: VMATT2 Patient Participant Information Sheet (Community)

Patient Information Sheet

Validating an adherence measuring tool and evaluating its feasibility as a profiling tool for personalised medicines optimisation interventions by pharmacists

[11/04/2019]

You are being invited to take part in a PhD project. Before you decide whether or not to take part, it is important for you to understand why the research is being carried out and what it will involve. Please take time to read the following information sheet carefully before deciding whether or not to participate. The project consists of completing a questionnaire that is used to assess how certain behaviours can have an impact on someone's ability to take medicines for a medical condition.

What is the purpose of the study?

The primary aim of this study is to determine what factors, related to patient behaviour may affect their ability to take their medicines.

Why have I been chosen?

You are an individual that takes regular medication for Type 2 Diabetes, and hence are part of the target audience for the study.

Do I have to take part?

No. This research study is done purely on a voluntary basis. If you choose to take part after reading this information sheet, you will be asked to sign an informed consent form. You will then be asked to complete the questionnaire. You are free to withdraw from this study at any point without disadvantage and without having to provide a reason. Any data collected prior to withdrawal will be erased following confirmation that you no longer wish to proceed with the study. Whether you participate or not, there will be no impact on your current treatment. We thank you for taking the time to read this information sheet even if you choose not to participate in the study.

What will happen to me if I take part?

You will be asked to complete a questionnaire that has been developed by the research team. The questionnaire includes statements about your diabetes medication and you will be asked to what degree you agree or disagree with these, as well as simple yes or no questions. There are no correct or incorrect answers for the questionnaires being completed. Please tick the box that applies most to you. These questions will be related to your thoughts on your Type 2 diabetes, as well as your thoughts on taking medicines among other related topics. You do not have to complete a question if you do not want to. Additionally, you will be asked about your most recent HbA1C result. If you know your HbA1c result, but do not want to provide an answer, you are under no obligation to do so and please skip this question. You will be asked to complete a few questions related to your age, gender and ethnicity. We will also ask you to provide some information on the type of medicines you take for diabetes

and any other medical conditions you may have. Throughout the process, your pharmacist will be able to answer any questions you may have

To better understand your relationship with your medicines, with your consent, your pharmacist will access information about the collection of your diabetes medication over the past 6 months.

Should you wish to take part in a follow-up study in 6 months, you can provide your contact details on the final page of the questionnaire. This page will be removed and stored securely by your pharmacist, who will then contact you again in 6 months to participate in the follow up study. If you choose to participate, you will be asked to complete the questionnaire and your pharmacist will again access information regarding the collection of your diabetes medication over the past 6 months. At no point will your contact details be passed onto the research team. Even if you choose to participate in the follow-up study at 6 months during the initial consultation with your pharmacist, you can later decline to participate without stating a reason when you are contacted.

What are the possible benefits of taking part?

Although there is no actual medical benefit from the study, you will be contributing to our understanding about why patients do or do not take their medicines, helping us to develop strategies to support medication adherence.

What are the possible disadvantages and risks of taking part?

There are no perceived disadvantages or risks. Your time is very valuable for this project and therefore if you do decide to take part this may take up to 10-20 minutes of your time for completion of the questionnaire. If you decide to participate in the follow-up at 6 months, you will be asked by your pharmacist to re-consent to taking part, and completing the questionnaire again. This process may take up to 20-30 minutes of your time.

What happens when the research study ends?

You will be under no obligation to volunteer again. Contact details for myself plus my project supervisor are included at the end of this information sheet should you wish to ***discuss the findings***.

Will my taking part be kept confidential?

All information collected during the course of the study will be kept strictly confidential and in secure storage. Responses will be anonymised before analysis so that it will not be possible to identify you or any other participant. Only I and the project supervisor will have access to this dataset which contains no confidential information. Only your pharmacist will have access to your contact details.

Any personal information collected will be immediately destroyed, except that required by the University research policy.

Should you wish to provide your contact details for further participation in the study, this information will be held with your pharmacist to maintain your confidentiality. If you choose to participate in a follow-up as part of the project, you will be contacted by your pharmacist. You can request to have this information removed at any point during the study. Upon

completion of the study, all contact information not usually kept by your pharmacist will be destroyed.

Who is organising and funding the study?

This study is part of my PhD project, within the School of Pharmacy, Faculty of Science, Engineering and Computing, at Kingston University. Observia, an e-health solution organisation based in France are the main sponsor for the project. None of the investigators stands to gain financially from this study.

What will happen to the results of the research study?

The results will be part of my thesis which will be made available in the Faculty of Science, Engineering and Computing Learning Resources Centre (library) at Kingston University for others to view. In addition, findings arising from this study may be presented at national and international conferences as well as published in scientific journals. It will not be possible to identify you or others from any such publications with results being aggregated for the whole group.

Please contact myself or my supervisor, Professor Reem Kayyali if you have any questions about this project. You are welcome to contact myself or Professor Kayyali on the emails detailed below should you require any further information or support following your participation in the study.

Who has reviewed the study?

The Kingston University Faculty of Science, Engineering and Computing Research Ethics Committee has reviewed and approved this study.

In addition, this project is being supervised by Professor Reem Kayyali and Philip Crilly

Contact for further information.
Further information may be obtained from:

Joshua Wells – k1213537@kingston.ac.uk

Reem Kayyali – r.kayyali@kingston.ac.uk
Work Telephone: 0208 417 2561
Work Address: Penrhyn Road, Kingston upon Thames, KT1 2EE

If you become concerned about any issue that may have been raised by you participating in this study, please contact myself or Professor Reem Kayyali

For any concerns relating to data protection please contact the university's Data Protection Officer on: dpo@kingston.ac.uk

Thank you for taking the time to read this information sheet.

Appendix O: VMATT2 Patient Consent Form (Hospital)

IRAS ID: **270768**

Study Number:

Participant Identification Number for this trial:

CONSENT FORM

Title of Project: **Validating a medication adherence tool in patients with Type 2 Diabetes**

Name of Researcher:

Please initial box

1. I confirm that I have read the information sheet dated ……. (version …….) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from Kingston University, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I understand that only the research team will have access to my contact information, and that all other information I provide will be anonymous. ☐

5. I agree that research data gathered for the study may be published provided that I cannot be identified as a subject. ☐

6. I give permission for the researcher to contact my community pharmacist to review my diabetes medication collection information over the previous 6 months. ☐

7. I agree to take part in the above study ☐

	Yes	No
8. I understand that by voluntarily providing my contact details, I agree to be contacted regarding future participation in the study by the lead researcher and that I can withdraw from this at any point during the study	☐	☐
	Yes	No

9. I agree to be contacted in 6 months to take part in this study again. ☐ ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Appendix P: VMATT2 Patient Participant Information Sheet (Hospital)

Validating a medication adherence tool in patients with Type 2 Diabetes

Patient Information Sheet

You are being invited to take part in a research study at Kingston Hospital. Joining the study is entirely your choice. Before you decide whether to take part, it is important for you to understand why the research is being carried out and what it will involve. Please take time to read the following information sheet carefully before deciding whether to participate. The researcher is available to answer any questions you may have.

Why is this research being done?

The main aim of this research is to better understand why patients with Type 2 Diabetes may take, or not take, their medicines. You have been invited to take part as you are a patient with Type 2 Diabetes that regularly takes medicine for this condition.

What will I be expected to do if I take part?

You will be asked to complete a questionnaire that has been developed by the research team. The questionnaire includes statements about your Diabetes medication and you will be asked to what degree you agree or disagree with these, as well as simple yes or no questions. These questions will be related to your thoughts on your Type 2 Diabetes, as well as your thoughts on taking medicines among other related topics. You will be asked to complete some questions about yourself, such as your gender, ethnicity, age and annual income. We will also ask you to provide some information on any other medical conditions you may have. Throughout the process, the researcher will be able to answer any questions you may have. Completing the questionnaire takes roughly 10-15 minutes to complete.

With your consent, the researcher will contact your community pharmacist for information about the collection of your diabetes

medication within the previous 6 months. This will enable us to better understand your relationship with your medicines.

Should you wish to take part in and consent to a follow-up study, your contact details will be taken and kept securely by the researcher. You will then be invited to complete a questionnaire 6 months later. In addition to the questionnaire, your community pharmacist will be contacted to request information regarding the collection of your diabetes medication over the past 6 months. The follow-up can be completed over the phone or in person, however if you prefer, we can send a postal copy of the survey to complete in the comfort of your home with a stamped return addressed envelope. This is optional, and you are able to withdraw or opt out of this part of the study at any point up until and including the follow-up call. Participation or decision to withdraw will not have any impact on the care you receive.

In addition, the researcher will review your medical notes to see how many hospital visits you make in the 6 months since you complete the first questionnaire. The researcher will collect this data in order to explore potential relationships between admissions to hospital and how patients take their medicines.

What are the possible benefits of taking part?

Although there is no actual medical benefit from the study, you will be contributing to our understanding about why patients do or do not take their medicines, helping us to develop strategies to support patients that may struggle with their medicines.

What are the possible disadvantages and risks of taking part?

There are no perceived disadvantages or risks. We realise your time is very valuable and participation in the study is estimated to take between 15-25 minutes for each occasion you complete the questionnaire.

What happens when the research study ends?

The anonymised data will be reviewed by the research team and a report will be written to summarise and highlight the findings. The results may be published in a respected journal and presented at professional meetings to share the outcome of the research. No information that could identify you will be included, and you will not be identified in any report or

publication. All information will be completely anonymised and stored securely at Kingston Hospital during and after the study.

Will my taking part be kept confidential?

All information collected during the study will be kept strictly confidential and in secure storage. Data will be stored securely on the Kingston Hospital Research and Development server in a password protected file with only access from the lead researcher. Responses will be anonymised before analysis so that it will not be possible to identify you or any other participant. Only the research team will have access to the anonymised data, and your contact details should you wish to participate in the follow-up study will be stored securely at Kingston Hospital. Any anonymised data collected will be stored securely at Kingston Hospital for a maximum of five years. The lead researcher, Josh Wells, will be responsible for control of the data at the Trust. Data storage will comply with all GDPR guidelines as outlined in the 2018 GDPR Regulation.

Who is organising and funding the study?

This study is part of a PhD project, with Kingston Hospital and the School of Pharmacy, Faculty of Science, Engineering and Computing, at Kingston University. Observia, an e-health solution organisation based in France are the main sponsor for the project. None of the investigators stand to gain financially from this study.

Who should I contact for more information or if I have concerns?

Josh Wells is the lead researcher for the project and will be responsible for data collection and storage. He is a qualified pharmacist and can answer any questions or concerns you may have regarding your participation in the study. His contact details are below:

Email: K1213537@kingston.ac.uk
Telephone: 07715630551

Should you wish to withdraw from the study at any time, you can do so any time without affecting your right to care. Please contact the researcher team to withdraw your consent to participate.

The Kingston Hospital Patient Advice and Liaison Service (PALS) are also available for support should you feel you want to make a complaint or have any concerns. The PALS contact details are included below:

Email: khft.pals@nhs.net
Telephone: 020 8934 3993

Thank you for taking the time to read this information sheet.

Appendix Q: VMATT2 SPUR Questionnaire

Validating a medication adherence tool in patient with Type 2 Diabetes

Dear participant,

We're doing a study to learn more about the ways that attitudes, beliefs, and behaviors predict the ways in which people take their diabetes medications. The goal of this work is to develop an adaptive electronic questionnaire which can accurately identify individuals with Type 2 diabetes who have difficulty taking their diabetes medications as prescribed. In order to help us understand why people may struggle with their diabetes medicines, we have designed this questionnaire.

This questionnaire contains four independent surveys. Some of these may seem slightly repetitive, however we aim to use a number of surveys to compare the results and links between them. While it may appear that there are a lot of questions, those who completed the survey on average took a maximum of 10-15 minutes.

Thank you for your time and agreeing to take part in this study.

Part 1 – Personal Information

Socio-demographic Information (Please tick the appropriate box for each question)

Age

25-29	
30-39	
40-49	
50-59	
60-69	
70-79	
80+	

Highest Level of Education

No formal education	
GCSE or Equivalent	
A-Level or Equivalent	
Bachelors Degree or Equivalent	
Post-graduate Degree or Equivalent	
Other (Please specify)	

Average Annual Income

>£14,999	
£15,000 - £24,999	
£25,000 - £34,999	
£35,000 - £44,999	
£45,000 - £54,999	
£55,000 - £64,999	
£65,000 - £74,999	
>£75,000	
Unemployed	
Retired	

Gender

Male	
Female	
Other	

Ethnicity

White	
Mixed / Multiple ethnic groups	
Asian / Asian British	
Black / African / Caribbean / Black British	
Other ethnic group (Please specify)	

Clinical History (Please provide details where known)

Weight (kg) – if known	
Height (cm) – if known	
BMI (kg/m^2) (Calculated by researcher)	
Most recent HbA1c result (%) – if known	

Medications taken for Diabetes e.g. Metformin	**How you take your medicine e.g. 1 tablet three times a day**

Medical Conditions (including Diabetes)

Part 2 – Questionnaires

SPUR Questionnaire *– Please choose the response that you feel best suits your personal situation. There are no right or wrong answers to any question.*

1. My diabetes affects my relationships with those I care about.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

2. My diabetes affects my social life.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

3. I would be interested in knowing if others with diabetes follow their treatment plan.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

4. I think that people with diabetes generally follow their doctors' prescription exactly.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

5. The people in my life help me manage my diabetes.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

6. Fighting for my health is my highest priority.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

7. Precisely following doctors’ recommendations is the best way for me to stay healthy.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

8. I trust doctors' recommendations.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

9. It is essential that I follow my treatment plan.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

10. Sometimes my diabetes seems unreal to me.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

11. I'm the kind of person who will follow their treatment plan exactly.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

12. I will have to take a treatment for my diabetes for the rest of my life.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

13. I live in the moment.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

14. If my doctor recommends that I do something, I do it.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

15. Sometimes doctors prescribe treatment you don't really need.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

16. Sometimes I don't follow my treatment plan exactly.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

17. I find it easy to get my treatment for my diabetes.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

18. I can easily pay for my treatment.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

19. I am able to follow my treatment plan.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

20. Too many doctors don’t listen to what patients tell them.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

21. My diabetes has led to financial problems.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

22. I find it easy to follow my treatment plan when I am not at home.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

23. I am satisfied with the level of information I have about my treatment.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

24. I find it easy to manage the different medications I take.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

25. I find it easy to take my medication for my diabetes.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

26. I am worried about the side effects of some medications.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

27. I believe I can stop my treatment for my diabetes when I feel better.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

28. I am worried about taking medications.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

29. My diabetes should be taken seriously.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

30. I am able to exercise despite my diabetes.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

31. My treatment affects my sex life.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

32. I am satisfied with the level of information I have about my diabetes.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

33. I completely understand my diabetes.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

34. I don't like taking medications.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

35. Medications for my diabetes don't do anything for me.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

36. My treatment helps my diabetes.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

37. There is no point in taking medications for my diabetes.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

38. What I do impacts my diabetes.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

39. My diabetes is likely to get worse if I don’t follow my treatment plan.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

40. I feel worse if I don't follow my treatment plan.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

41. Medications are more expensive than they should be.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

42. My diabetes keeps me from doing things I want to do.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

43. Following my diabetes treatment plan lets me do the things I want to do.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

44. Non-traditional treatments could replace some of my medications.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

45. I have found ways to deal with my diabetes.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

MARS Questionnaire *- We are interested in your experiences taking medications. There is no right or wrong answer. Please answer each question based on your personal experience with your diabetes medication.*

11. Do you ever forget to take your diabetes medication?

Yes ☐ **No** ☐

12. Are you careless at times at taking medication for your diabetes?

Yes ☐ **No** ☐

13. When you feel better do you sometimes stop taking your diabetes medication?

Yes ☐ **No** ☐

14. Sometimes if you feel worse when you take the diabetes medication do you stop taking it?

Yes ☐ **No** ☐

15. I take my diabetes medication only when I am sick

Yes ☐ **No** ☐

16. It is unnatural for my mind and body to be controlled by diabetes medication

Yes ☐ **No** ☐

17. My thoughts are clearer on diabetes medication

Yes ☐ **No** ☐

18. By staying on diabetes medication, I can prevent getting sick

Yes ☐ **No** ☐

19. I feel weird, like a zombie, on diabetes medication

Yes ☐ **No** ☐

20. Diabetes medication makes me feel tired and sluggish

Yes ☐ **No** ☐

BMQ Questionnaire *- We would like to ask you about your personal views about medicines prescribed for your diabetes. Please indicate the extent to which you agree or disagree with each statement. There are no right or wrong answers. We are only interested in your personal views.*

1. My health at present depends on my diabetes medicines

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

2. Having to take diabetes medication worries me

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

3. My life would be impossible without my diabetes medication

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

4. Without my diabetes medication I would be very ill

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

5. I sometimes worry about the long term effects of my diabetes medication

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

6. My diabetes medication is mystery to me

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

7. My health in the future will depend on my diabetes medication

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

8. My diabetes medication disrupts my life

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

9. I sometimes worry about becoming too dependent on my diabetes medication

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

10. My diabetes medication protects me from becoming worse.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

BMQ-General

- We would like to ask you about your personal views about medicines in general.
- These are statements other people have made about medicines in general.
- Please indicate the extent to which you agree or disagree with them by ticking the appropriate box.
- There are no right or wrong answers.
- Please only tick one box per question.

11. Doctors use too many medicines

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

12. People who take medicines should stop their treatment for a while every now and again.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

13. Most medicines are addictive.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

14. Natural remedies are safer than medicines

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

15. Medicines do more harm than good.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

16. All medicines are poisons

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

17. Doctors place too much trust on medicines

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

18. If doctors had more time with patients they would prescribe fewer medicines.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

DTSQ-s Questionnaire *- The following questions are concerned with the treatment of your diabetes (including insulin, tablets, and/or diet) and your experience over the past few weeks.*

1. How satisfied are you with your current treatment?

☐	☐	☐	☐	☐	☐	☐
0	**1**	**2**	**3**	**4**	**5**	**6**
Very dissatisfied						Very satisfied

2. How often have you felt that your blood sugars have been unacceptably high recently?

☐	☐	☐	☐	☐	☐	☐
0	**1**	**2**	**3**	**4**	**5**	**6**
None of the time						Most of the time

3. How often have you felt that your blood sugars have been unacceptably low recently?

☐	☐	☐	☐	☐	☐	☐
0	**1**	**2**	**3**	**4**	**5**	**6**
None of the time						Most of the time

4. How convenient have you been finding your treatment recently?

☐ ☐ ☐ ☐ ☐ ☐ ☐

0 1 2 3 4 5 6

Very inconvenient Very convenient

5. How flexible have you been finding your treatment to be recently?

☐ ☐ ☐ ☐ ☐ ☐ ☐

0 1 2 3 4 5 6

Very inflexible Very flexible

6. How satisfied are you with your understanding of your diabetes?

☐ ☐ ☐ ☐ ☐ ☐ ☐

0 1 2 3 4 5 6

Very dissatisfied Very satisfied

7. Would you recommend this form of treatment to someone else with your kind of diabetes?

☐ ☐ ☐ ☐ ☐ ☐ ☐

0 1 2 3 4 5 6

No, definitely not Yes, definitely

8. How satisfied would you be to continue with your present form of treatment?

☐ ☐ ☐ ☐ ☐ ☐ ☐

0 1 2 3 4 5 6

Very dissatisfied Very satisfied

Part 3 – End of Questionnaire

Dear participant,

Thank you for completing our study questionnaire. Please now return the completed questionnaire to the researcher and ensure the following items have also been completed (please tick the appropriate box):

- ☐ You have signed and returned your consent form to the pharmacist
- ☐ You have a copy of the patient information sheet provided
- ☐ If you wish, please complete the follow up details on the page 13

If you have any questions or concerns, or would like some more information regarding the study, please refer to the contact details provided for the research team on the patient information sheet.

Researcher Use Only

Please complete the following information below relating to the participant's previous diabetes medication refill as shown in the table over the past 6 months.

Time Period	Diabetes Medicines Collected	Amount Supplied e.g. 30 days	Date Supplied
Month 1			
Month 2			
Month 3			
Month 4			
Month 5			
Month 6			

Please complete the details below: Only the lead researcher will have access to this information.

Should you choose to provide your contact information, the researcher will contact you for a 6 month follow up.

Personal Contact Details

Full Name	
D.O.B	
Mobile Number	
Home Number	
Email Address	

Study Number	Patient Ref. Number

If you have any concerns following completion of this questionnaire, please speak to your pharmacist or a medical professional for support.

Appendix R: VMATC Pilot Patient Consent Form

WRITTEN CONSENT TO PARTICIPATE IN A RESEARCH STUDY (for patients)

Statement by participant

- I confirm that I have read and understood the information sheet/letter of invitation for this study. I have been informed of the purpose, risks, and benefits of taking part.

Validating an adherence measuring tool and evaluating its feasibility as a profiling tool for personalised medicines optimisation interventions by pharmacists – Pilot Study

- I understand what my involvement will entail and any questions have been answered to my satisfaction.
- I understand that my participation is entirely voluntary, and that I can withdraw at any time without prejudice.
- I understand that all information obtained will be confidential.
- I agree that research data gathered for the study may be published provided that I cannot be identified as a subject.
- Contact information has been provided should I (a) wish to seek further information from the investigator at any time for purposes of clarification (b) wish to make a complaint.

Participant's Signature----------

Date ----------

Statement by investigator

- I have explained this project and the implications of participation in it to this participant without bias and I believe that the consent is informed and that he/she understands the implications of participation.

Name of investigator Joshua Sterling Wells

Signature of investigator ----------

Date ----------

Appendix S: VMATC Pilot Patient Participant Information Sheet

Patient Information Sheet

Validating an adherence measuring tool and evaluating its feasibility as a profiling tool for personalised medicines optimisation interventions by pharmacists – Pilot Study

[19/12/2019]

You are being invited to take part in a PhD pilot project. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information sheet carefully before deciding whether or not to participate. The project consists of completing a prototype questionnaire that is used to assess how certain behaviour can impact the ability to take medicines for a medical condition.

What is the purpose of the study?

The primary aim of this study is to determine what factors related to patient behaviour may affect their ability to take their medicines.

Why have I been chosen?

You represent an individual that falls into a key stakeholder category identified at the start of the project as a target audience for the study. More specifically, you are an individual that takes regular medication for Chronic Obstructive Pulmonary Disease (COPD).

Do I have to take part?

No. This research study is done purely on a voluntary basis. If you choose to take part after reading this information sheet, we will continue with the session. Before completing any activities, I will ask you to sign an informed consent. You are free to withdraw from this study at any point without disadvantage and without having to provide a reason. Any data collected prior to withdrawal will be erased on confirmation you no longer wish to proceed with the study.

What will happen to me if I take part?

You will be asked to complete a questionnaire that has been developed by the research team. The questionnaire includes statements and you will be asked to what degree to you agree or disagree, ticking the box that applies most to you. These questions will be related to your thoughts on your COPD, as well as your thoughts on taking medicines among other related topics. Additionally, you will be asked to highlight questions e.g. you may not want to answer these questions or find them challenging. You do not have to complete a question if you do not want to. Finally, you will be asked to complete a few questions related to your demographic information such as your age range. Throughout the process the lead researcher will be available to answer any questions you may have.

What are the possible benefits of taking part?

Although there is no actual medical benefit from the study, you will be providing input to a university PhD research project as well as developing research in the area of medication adherence. Your contribution to this project will help shape the future of the research in terms of the direction for moving forwards e.g. potential applications for real-time assessment of patient adherence in chronic conditions to help develop tools to improve patient medication taking behaviours and hopefully their quality of life.

What are the possible disadvantages and risks of taking part?

There are no perceived disadvantages or risks. Your time is very valuable for this project and therefore if you do decide to take part this may take up to 15-20 minutes of your time.

What happens when the research study ends?

You will be under no obligation to volunteer again. Contact details for myself plus project supervisor are included at the end of this information sheet should you wish to ***discuss the findings***.

Will my taking part be kept confidential?

All information collected during the course of the study will be kept strictly confidential and in secure storage. Responses will be anonymised before analysis so that it will not be possible to identify you or any other participant. Only I and the project supervisor will have access to this dataset.

Any personal information collected will be immediately destroyed, except that required by the University research policy.

Who is organising and funding the study?

This study is part of my PhD project, within the School of Pharmacy, Faculty of Science, Engineering and Computing, at Kingston University. Observia, an e-health solution organisation based in France are the main sponsor for the project. None of the investigators stands to gain financially from this study.

What will happen to the results of the research study?

The results will be part of my thesis which will be made available in the Faculty of Science, Engineering and Computing Learning Resources Centre (library) at Kingston University for others to view. In addition, findings arising from this study may be presented at national and international conferences as well as published in scientific journals. It will not be possible to identify you or others from any such publications with results being aggregated for the whole group. In such cases where an interview is used, if you permit for the interview to be recorded and transcribed, participants will always be referred to by pseudonyms.

Please contact myself or my supervisor, Professor Reem Kayyali if you have any questions about this project. You are welcome to contact myself or Professor Kayyali on the emails detailed below should you require any further information or support following your participation in the study.

Who has reviewed the study?

The Kingston University Faculty of Science, Engineering and Computing Research Ethics Committee has reviewed and approved this study.

In addition, this project is being supervised by Professor Reem Kayyali and Philip Crilly

Contact for further information.
Further information may be obtained from:

Joshua Wells – k1213537@kingston.ac.uk

Reem Kayyali – r.kayyali@kingston.ac.uk

If you become concerned about any issue that may have been raised by you participating in this study, please contact myself or Professor Reem Kayyali

For any concerns relating to data protection please contact the university's Data Protection Officer i.e. dpo@kingston.ac.uk

Thank you for taking the time to read this information sheet.

Appendix T: VMATC Pilot Questionnaire

Dear participant,

Please read the following information carefully.

Please complete the following questionnaire by ticking the box for each statement that best applies to you. There is no time-limit for completion of the questionnaire, and the researcher is available to answer any additional questions you may have. There will be an opportunity to provide feedback after completion of the questionnaire. We estimate the questionnaire will take 10-15 minutes to complete.

Please use the colour marker provided to highlight any question that you have concerns with e.g. find it difficult to answer/are unable to provide an answer for. There is a small box at the end of the questionnaire where you can provide feedback on the questions you may have highlighted during completion.

Thank you for agreeing to take part in the session.

For each sentence, please tick the box that best applied to you.

1. **My COPD affects my relationships with those I care about.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

2. **My COPD affects my social life.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

3. **I would be interested in knowing if others with COPD follow their treatment plan.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

4. **I think that people with COPD generally follow their doctors' prescription exactly.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

5. **The people in my life help me manage my COPD.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

6. **Fighting for my health is my highest priority.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

7. **Precisely following doctors' recommendations is the best way for me to stay healthy.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

8. **I trust doctors' recommendations.**

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

9. It is essential that I follow my treatment plan.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

10. Sometimes my COPD seems unreal to me.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

11. I'm the kind of person who will follow their treatment plan exactly.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

12. I will have to take a treatment for my COPD for the rest of my life.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

13. I live in the moment.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

14. If my doctor recommends that I do something, I do it.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

15. Sometimes doctors prescribe treatment you don't really need.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

16. Sometimes I don't follow my treatment plan exactly.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

17. I find it easy to get my treatment for my COPD.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

18. I can easily pay for my treatment.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

19. I am able to follow my treatment plan.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

20. Too many doctors don't listen to what patients tell them.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

21. My COPD has led to financial problems.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

22. I find it easy to follow my treatment plan when I am not at home.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

23. I am satisfied with the level of information I have about my treatment.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

24. I find it easy to manage the different medications I take.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

25. I find it easy to take my medication for my COPD.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

26. I am worried about the side effects of some medications.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

27. I believe I can stop my treatment for my COPD when I feel better.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

28. I am worried about taking medications.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

29. My COPD should be taken seriously.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

30. I am able to exercise despite my COPD.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

31. My treatment affects my sex life.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

32. I am satisfied with the level of information I have about my COPD.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

33. I completely understand my COPD.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

34. I don't like taking medications.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

35. Medications for my COPD don't do anything for me.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

36. My treatment helps my COPD.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

37. There is no point in taking medications for my COPD.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

38. What I do impacts my COPD.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

39. My COPD is likely to get worse if I don’t follow my treatment plan.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

40. I feel worse if I don't follow my treatment plan.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

41. Medications are more expensive than they should be.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

42. My COPD keeps me from doing things I want to do.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

43. Following my COPD treatment plan lets me do the things I want to do.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

44. Non-traditional treatments could replace some of my medications.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

45. I have found ways to deal with my COPD.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

1. The questions were easy to answer

Strongly Disagree 1	Disagree 2	Neither Agree Nor Disagree 3	Agree 4	Strongly Agree 5

2. I am happy with the length of the questionnaire

Strongly Disagree 1	Disagree 2	Neither Agree Nor Disagree 3	Agree 4	Strongly Agree 5

3. I would be happy to complete the questionnaire by myself

Strongly Disagree 1	Disagree 2	Neither Agree Nor Disagree 3	Agree 4	Strongly Agree 5

4. I believe this questionnaire could help improve my relationship with my medicines

Strongly Disagree 1	Disagree 2	Neither Agree Nor Disagree 3	Agree 4	Strongly Agree 5

5. The questions are relevant to my condition

Strongly Disagree 1	Disagree 2	Neither Agree Nor Disagree 3	Agree 4	Strongly Agree 5

6. Any additional comments?

Demographic Questions

Age Gender

25-29	
30-39	
40-49	

Male	
Female	
Other	

50-59	
60-69	
70-79	
80+	

Highest Level of Education

No formal education	
GCSE or Equivalent	
A-Level or Equivalent	
Bachelors Degree or Equivalent	
Post-graduate Degree or Equivalent	
Other (Please specify)	

Ethnicity

White	
Mixed / Multiple ethnic groups	
Asian / Asian British	
Black / African / Caribbean / Black British	
Other ethnic group (Please specify)	

Thank you for your time. Please return the completed questionnaire to the researcher who will be happy to answer any questions you may have.

Appendix U: VMATC Patient Consent Form

IRAS ID: **285590**

Study Number:

Participant Identification Number for this trial:

CONSENT FORM

Title of Project: A feasibility study to validate the SPUR questionnaire as a model to measure adherence and the impact of readmission in COPD (VMATC)

Name of Researcher:

Please initial box

4. I confirm that I have read the information sheet dated ……. (version …….) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

5. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

6. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from Kingston University, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I understand that only the research team will have access to my contact information, and that all other information I provide will be anonymous, including information about myself and my questionnaire responses. ☐

5. I agree that research data gathered for the study may be published provided that I cannot be identified as a subject. ☐

6. I give permission for the researcher to contact my community pharmacist and for them to share information about my COPD medication collection over the previous 6 months. ☐

Yes No

7. I give permission for the researcher to access my Summary Care Record for them to collect information about my COPD medication collection over the previous 6 months ☐ ☐

7. I agree to take part in the above study ☐

Yes No

8. I understand that by voluntarily providing my contact details, I agree to be contacted regarding ☐ ☐

future participation in the study by the lead researcher and that I can withdraw from this at any point during the study

Yes No

9. I agree to be contacted in 6 months to take part in this study again.

Yes No

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Appendix V: VMATC Patient Participant Information Sheet

A feasibility study to validate the SPUR questionnaire as a model to measure adherence and the impact of readmission in COPD

Patient Information Sheet

You are being invited to take part in a research study at Kingston Hospital. Joining the study is entirely your choice. Before you decide whether to take part, it is important for you to understand why the research is being carried out and what it will involve. Please take time to read the following information sheet carefully before deciding whether to participate. The researcher is available to answer any questions you may have.

Why is this research being done?

The main aim of this research is to better understand why patients with COPD may take, or not take, their medicines.

Why have I been chosen?

You have been invited to take part as you are a patient with COPD that regularly takes medicine for this condition.

Do I have to take part?

No. This research study is done purely on a voluntary basis. Should you decide to participate, you are free to withdraw from this study at any point without disadvantage and without having to provide a reason.

What will I be expected to do if I take part?

You will be asked to complete a questionnaire that has been developed by the research team. The questionnaire includes statements about your COPD medication and you will be asked to what degree you agree or disagree with these, as well as simple yes or no questions. These questions will be related to your thoughts on your COPD, as well as your thoughts on taking medicines among other related topics. You will be asked to complete some questions about yourself, such as your gender, ethnicity, age and annual income. We will also ask you to provide some information on any other medical conditions you may have. Throughout the process, the researcher will be able to answer any questions you may have. Completing the questionnaire takes roughly 10-15 minutes to complete.

With your consent, the researcher will either contact your community pharmacist or access your Summary Care Record for information about the collection of your COPD medication within the previous 6 months. This will enable us to better understand your relationship with your medicines.

Should you wish to take part in and consent to a follow-up study, your contact details will be taken and kept securely by the researcher. You will then be invited to complete a questionnaire 6 months later. In addition to the questionnaire, your community pharmacist will be contacted or SCR accessed to obtain information regarding the collection of your COPD medication over the past 6 months. The follow-up can be completed over the phone or in person, however if you prefer,

we can send a postal copy of the survey to complete in the comfort of your home with a stamped return addressed envelope. This is optional, and you are able to withdraw or opt out of this part of the study at any point up until and including the follow-up call. Participation or decision to withdraw will not have any impact on the care you receive.

In addition, the researcher will review your medical notes to see how many hospital visits you make in the 6 months since you complete the first questionnaire. The researcher will collect this data in order to explore potential relationships between admissions to hospital and how patients take their medicines.

What are the possible benefits of taking part?

Although there is no actual medical benefit from the study, you will be contributing to our understanding about why patients do or do not take their medicines, helping us to develop strategies to support patients that may struggle with their medicines.

What are the possible disadvantages and risks of taking part?

There are no perceived disadvantages or risks. We realise your time is very valuable and participation in the study is estimated to take between 15-25 minutes for each occasion you complete the questionnaire.

What happens if I lose the capacity to consent during the study?

Participants will be asked to provide informed consent at both the initial, and follow-up stages of data collection, should they wish to participate. If for any reason a participant is unable to make an informed decision about their continued participation in the follow-up study, they would be removed from the study and not included in the follow-up data collection. However, any data collected before this point, for example at the initial completion of the study questionnaire, will have been anonymised and therefore will be retained for the study.

What happens when the research study ends?

The anonymised data will be reviewed by the research team and a report will be written to summarise and highlight the findings. The results may be published in a respected journal and presented at professional meetings to share the outcome of the research. No information that could identify

you will be included, and you will not be identified in any report or publication. All information will be completely anonymised and stored securely at Kingston Hospital during and after the study.

Will my taking part be kept confidential?

All information collected during the study will be kept strictly confidential and in secure storage. Data will be stored securely on the Kingston Hospital Research and Development server in a password protected file with only access from the lead researcher. Responses will be anonymised before analysis so that it will not be possible to identify you or any other participant. Only the research team will have access to the anonymised data, and your contact details should you wish to participate in the follow-up study will be stored securely at Kingston Hospital. Any anonymised data collected will be stored securely at Kingston Hospital for a maximum of five years. The lead researcher, Josh Wells, will be responsible for control of the data at the Trust. Data storage will comply with all GDPR guidelines as outlined in the 2018 GDPR Regulation.

Who is organising and funding the study?

This study is part of a PhD project, with Kingston Hospital and the School of Pharmacy, Faculty of Science, Engineering and Computing, at Kingston University. Observia, an e-health solution organisation based in France are the funder for the project. Observia have in part contributed to some costs involved in the organisation of this study. None of the investigators stand to gain financially from this study.

Who should I contact for more information or if I have concerns?

Josh Wells is the lead researcher for the project and will be responsible for data collection and storage. He is a qualified pharmacist and can answer any questions or concerns you may have regarding your participation in the study. His contact details are below:

Email: K1213537@kingston.ac.uk
Telephone: 07715630551

Should you wish to withdraw from the study at any time, you can do so any time without affecting your right to care. Please contact the research team to withdraw your consent to participate.

The Chief Investigator based at Kingston University for this study is also available for support should you feel you want to make a complaint or have any concerns that cannot be answered by the lead researcher. Their contact details are included below:

Professor Reem Kayyali
Email: r.kayyali@kingston.ac.uk
Telephone: 0208 417 2561

Appendix W: VMATC SPUR Questionnaire

Validating a medication adherence tool in patients with chronic obstructive pulmonary disease (COPD)

Dear participant,

Type of residence

Home alone		
With a family member		
Care home	**Residential**	
	Nursing	
Other (please specify)		

We're doing a study to learn more about the ways that attitudes, beliefs, and behaviors predict the ways in which people take their COPD medications. The goal of this work is to develop an adaptive electronic questionnaire which can accurately identify individuals with COPD who have difficulty taking their COPD medications as prescribed. In order to help us understand why people may struggle with their COPD medicines, we have designed this questionnaire.

While it may appear that there are a lot of questions, those who completed the survey on average took a maximum of 10-15 minutes.

Thank you for your time and agreeing to take part in this study.

Part 1 – Personal Information

Socio-demographic Information (Please tick the appropriate box for each question)

Age

18-29	
30-39	
40-49	
50-59	
60-69	
70-79	
80-89	
90+	

Gender

Male	
Female	
Other	

Marital Status

Single	
Married	
Divorced/Separated	
Widow / widower	
Civil Partnership	

Ethnicity

White	
Mixed / Multiple ethnic groups	
Asian / Asian British	
Black / African / Caribbean / Black British	
Other ethnic group (Please specify)	

£15,000 - £24,999	
£25,000 - £34,999	
£35,000 - £44,999	
£45,000 - £54,999	
£55,000 - £64,999	
£65,000 - £74,999	
>£75,000	
Unemployed	
Retired	

Highest Level of Education

No formal education	
GCSE or Equivalent	
A-Level or Equivalent	
Bachelors Degree or Equivalent	
Post-graduate Degree or Equivalent	
Other (Please specify)	

Smoking status

Smoker		**How many cigarettes do you smoke a day?**	
Ex-smoker		**How many years ago did you stop smoking?**	
		How many cigarettes do you smoke a day?	
Non-smoker			
E-cigarette smoker			

Medications taken for COPD eg. Salmeterol	**How you take your medicine e.g. 1 puff twice a day**

Medical Conditions (including COPD)

Have you received the influenza vaccine this year?
Yes ☐ **No** ☐

How many inhalers do you use? _____

Has a health care professional checked your inhaler technique?

Yes ☐ **No** ☐

If yes how long ago was it? _____

How many times in a year do you visit your general practitioner (GP) concerning your COPD?

_____

Have you had an exacerbation (flare up) of your COPD in the last year?

Yes ☐ **No** ☐

If yes, how many times? _____

How many rescue packs (antibiotic + steroid) have you used in the last year? _____

Have you previously been admitted to Kingston Hospital?

Yes ☐ **No** ☐

If yes how many times in the last year? _____

During this or previous admission to Kingston hospital, have you received any counselling/education on COPD?

Yes, during this admission ☐ **Yes, during a previous admission** ☐ **No** ☐

If yes who provided this education? _____

During this or previous admission to Kingston hospital, have you received any counselling/education on how to use your inhaler(s) correctly?

Yes, during this admission ☐ **Yes, during a previous admission** ☐ **No** ☐

If yes who provided this education? _____

Part 2 – Questionnaires

CAT Score For each item below, place a mark (X) in the box that best describes your current situation. Please ensure that you only select one response for each question

☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I never cough					I cough all the time

☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I have no phlegm (mucus) on my chest at all					My chest is full of phlegm (mucus)

☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
My chest does not feel tight at all					My chest feels very tight

0	1	2	3	4	5
When I walk up a hill or a flight of stairs I am not out of breath					When I walk up a hill or a flight of stairs I am completely out of breath

0	1	2	3	4	5
I am not limited to doing any activities at home					I am completely limited to doing all activities at home

0	1	2	3	4	5
I am confident leaving my home despite my lung condition					I am not confident leaving my home at all because of my lung condition

0	1	2	3	4	5
I sleep soundly					I do not sleep soundly because of my lung condition

0	1	2	3	4	5
I have lots of energy					I have no energy at all

SPUR Questionnaire *– Please choose the response that you feel best suits your personal situation. There are no right or wrong answers to any question.*

1. **My COPD affects my relationships with those I care about.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

2. **My COPD affects my social life.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

3. **I would be interested in knowing if others with COPD follow their treatment plan.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

4. **I think that people with COPD generally follow their doctors' prescription exactly.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

5. **The people in my life help me manage my COPD.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

6. **Fighting for my health is my highest priority.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

7. **Precisely following doctors' recommendations is the best way for me to stay healthy.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

8. **I trust doctors' recommendations.**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

9. It is essential that I follow my treatment plan.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

10. Sometimes my COPD seems unreal to me.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

11. I'm the kind of person who will follow their treatment plan exactly.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

12. I will have to take a treatment for my COPD for the rest of my life.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

13. I live in the moment.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

14. If my doctor recommends that I do something, I do it.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

15. Sometimes doctors prescribe treatment you don't really need.

☐	☐	☐	☐	☐
1	2	3	4	5
I strongly disagree				I strongly agree

16. Sometimes I don't follow my treatment plan exactly.

☐	☐	☐	☐	☐
1	2	3	4	5

I strongly disagree I strongly agree

17. I find it easy to get my treatment for my COPD.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
I strongly disagree I strongly agree

18. I can easily pay for my treatment.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
I strongly disagree I strongly agree

19. I am able to follow my treatment plan.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
I strongly disagree I strongly agree

20. Too many doctors don't listen to what patients tell them.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
I strongly disagree I strongly agree

21. My COPD has led to financial problems.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
I strongly disagree I strongly agree

22. I find it easy to follow my treatment plan when I am not at home.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
I strongly disagree I strongly agree

23. I am satisfied with the level of information I have about my treatment.

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5
I strongly disagree I strongly agree

24. I find it easy to manage the different medications I take.

☐ ☐ ☐ ☐ ☐

1	2	3	4	5
I strongly disagree				I strongly agree

25. I find it easy to take my medication for my COPD.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

26. I am worried about the side effects of some medications.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

27. I believe I can stop my treatment for my COPD when I feel better.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

28. I am worried about taking medications.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

29. My COPD should be taken seriously.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

30. I am able to exercise despite my COPD.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

31. My treatment affects my sex life.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

32. I am satisfied with the level of information I have about my COPD.

☐	☐	☐	☐	☐

1	2	3	4	5
I strongly disagree				I strongly agree

33. I completely understand my COPD.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

34. I don't like taking medications.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

35. Medications for my COPD don't do anything for me.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

36. My treatment helps my COPD.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

37. There is no point in taking medications for my COPD.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

38. What I do impacts my COPD.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

39. My COPD is likely to get worse if I don’t follow my treatment plan.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

40. I feel worse if I don't follow my treatment plan.

☐ ☐ ☐ ☐ ☐

1	2	3	4	5
I strongly disagree				I strongly agree

41. Medications are more expensive than they should be.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

42. My COPD keeps me from doing things I want to do.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

43. Following my COPD treatment plan lets me do the things I want to do.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

44. Non-traditional treatments could replace some of my medications.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

45. I have found ways to deal with my COPD.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
I strongly disagree				I strongly agree

Inhaler Adherence Scale

During the last three months have you:

1. Been careless about using your inhaler?

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Most of the time		some of the time		None of the time

2. Ever forgotten to use your inhaler?

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Most of the time some of the time None of the time

3. Ever stopped using your inhaler because you felt better?

☐ ☐ ☐ ☐ ☐

1 2 3 4 5

Most of the time some of the time None of the time

4. Used your inhaler less than your doctor prescribed because you felt better?

☐ ☐ ☐ ☐ ☐

1 2 3 4 5

Most of the time some of the time None of the time

Part 3 – End of Questionnaire

Dear participant,

Thank you for completing our study questionnaire. Please now return the completed questionnaire to the researcher and ensure the following items have also been completed (please tick the appropriate box):

- ☐ You have signed and returned your consent form to the pharmacist
- ☐ You have a copy of the patient information sheet provided

If you have any questions or concerns, or would like some more information regarding the study, please refer to the contact details provided for the research team on the patient information sheet.

Researcher Use Only

Please complete the following information below relating to the participant's previous COPD medication refill as shown in the table over the past 6 months.

Time Period	COPD Medicines Collected	Amount Supplied e.g. 30 days	Date Supplied
Month 1			
Month 2			
Month 3			
Month 4			
Month 5			
Month 6			
