CONFIRMATORY FACTOR ANALYSIS OF THE MALAYSIA MEDICATION ADHERENCE ASSESSMENT TOOL (MYMAAT) AMONG PATIENTS WITH CHRONIC MEDICATIONS

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CONFIRMATORY FACTOR ANALYSIS OF THE MALAYSIA MEDICATION ADHERENCE ASSESSMENT TOOL (MYMAAT) AMONG PATIENTS WITH CHRONIC MEDICATIONS

by

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TABLE OF CONTENTS

ACKNOWLEDGEMENT ..... **iiii**

TABLE OF CONTENTS ..... **iiiii**

LIST OF TABLES ..... **ix**

LIST OF FIGURES ..... **xi**

LIST OF SYMBOLS ..... **xiixii**

LIST OF ABBREVIATIONS ..... **xiii**

LIST OF APPENDICES ..... **xv**

ABSTRAK ..... **xvi**

ABSTRACT ..... **xviii**

CHAPTER 1 INTRODUCTION **1**

1.1 Background of the Study 1

1.1.1 Epidemiology of Medication Adherence 1

1.1.2 Impact of Medication Non-Adherence 3

1.1.3 Importance of Non-Adherence Identification 5

1.2 Problem Statement 7

1.3 Justification of Study 7

1.4 Significance of Study 8

1.5 Research Question 9

1.6 Research Objectives 9

1.6.1 General Objective 9

1.6.2 Specific Objectives 10

1.7 Research Hypothesis 10

CHAPTER 2 LITERATURE REVIEW **11**

2.1 Chronic Medication 11

2.1.1 Definitions 11

2.1.2 Epidemiology 11
2.2 Medication Adherence 12
2.2.1 Definition 12
2.2.2 Type 12
2.2.3 Measurement Tool 14
2.2.3(a) Traditional 14
2.2.3(b) New Technology 16
2.2.4 Scoring 18
2.2.5 Factor 19
2.2.5(a) Social and Economy 19
2.2.5(b) Therapy-Related Factor 21
2.2.5(c) Patient-Related Factor 22
2.3 Medication Adherence Questionnaires 22
2.3.1 MyMAAT 22
2.3.2 Malay version of the MMAS-8 24
2.4 Conceptual Framework ..... **Error! Bookmark not defined.**
2.4.1 Specific Medication-Taking Behaviour **Error! Bookmark not defined.**
2.4.2 Social-Cognitive Theory ..... **Error! Bookmark not defined.**
2.5 Chapter Summary 31
CHAPTER 3 METHODOLOGY 32
3.1 Introduction 32
3.2 Study Design 32
3.3 Study Duration and Location 32
3.4 Study Population and Sample 32
3.4.1 Reference Population 32
3.4.2 Source Population 32
3.4.3 Sampling Frame 33

3.4.3(a) Inclusion Criteria. 33
3.4.3(b) Exclusion Criteria. 33
3.4.4 Sample Size Calculation 34
3.4.5 Sampling Method and Study Subject 35
3.5 Variable Definition/ Ascertainment 37
3.5.1 Latent Variable 37
3.5.2 Measured Variable 37
3.6 Operational Definition 39
3.7 Measurement Tools 39
3.7.1 Questionnaires 39
3.7.1(a) Socio-Demographic Tool. 39
3.7.1(b) MyMAAT. 40
3.7.1(c) Malay version of the MMAS-8 40
3.8 Data Collection Method 43
3.9 Statistical Analyses 44
3.9.1 Descriptive Statistical Analysis 45
3.9.2 Confirmatory Factor Analysis (CFA) 45
3.9.2(a) Assumption Checking. 45
3.9.2(b) Measurement Model Specification. 46
3.9.2(c) Model Identification. 48
3.9.2(d) Fit Indices. 48
3.9.2(e) Model Re-Specification 51
3.9.2(f) Construct Reliability. 52
3.9.2(g) Construct Validity. 52
3.9.2(h) Convergent Validity 52
3.9.2(i) Average Variance Extracted (AVE). 53
3.9.2(j) Discriminant Validity 53

3.9.3 Convergent Validity With Other Instrument 55
3.9.4 Clinical Agreement 55
3.10 Study Flowchart 56
3.11 Ethical Consideration 57
3.11.1 Approval 57
3.11.2 Vulnerability of the Participants 57
3.11.3 Risks 58
3.11.4 Declaration of Conflict of Interest 58
3.11.5 Community Sensitivities and Benefits 58
3.11.6 Honorarium and Incentives 58
3.11.7 Direct Benefit to Participants 58
3.11.8 Privacy and Confidentiality 59
3.11.9 Publication Policy 59

CHAPTER 4 RESULTS 60
4.1 Introduction 60
4.2 Confirmatory Factor Analysis (CFA) Results 60
4.2.1 Preliminary Data Analysis 60
4.2.1(a) Response Rate 60
4.2.1(b) Missing Data. 60
4.2.1(c) Outliers 61
4.2.2 Participants' Demographic Characteristics 61
4.2.3 Overview of Study Variables 62
4.2.3(a) Factor 1 63
4.2.3(b) Factor 2. 66
4.2.4 Assumptions Checking 68
4.2.4(a) Univariate Normality 68
4.2.4(b) Multivariate Normality. 68

4.2.4(c) Positive Definiteness. 70

4.2.5 Measurement Models for the Malay version of the MyMAAT 70

4.2.5(a) Internal Structure 70

4.2.5(b) Convergent Validity and Construct Reliability 75

4.2.5(c) Discriminant Validity 76

4.2.6 Measurement Models for the English version of the MyMAAT 78

4.2.6(a) Internal Structure 78

4.2.6(b) Convergent Validity and Construct Reliability 83

4.2.6(c) Discriminant Validity 84

4.3 Convergent Validity With Other Instrument 86

4.3.1 Preliminary Data Analysis 86

4.3.1(a) Response Rate 86

4.3.1(b) Missing Data. 86

4.3.1(c) Outliers 86

4.3.2 Participants' Demographic Characteristics 86

4.3.3 Overview of Study Variables 88

4.3.3(a) Malay version of the MyMAAT 88

4.3.3(b) Malay version of the MMAS-8 88

4.3.3(c) Crosstabulation of the Malay version of the MyMAAT and the Malay version of the MMAS-8 88

4.3.4 Assumptions Checking 89

4.3.5 Correlation Testing 89

4.4 Clinical Agreement 91

4.4.1 Response Rate 91

4.4.2 Missing Data 91

4.4.3 Intraclass Correlation Coefficient (ICC) 91

4.5 Summary 92

CHAPTER 5 DISCUSSION 94

5.1 Introduction 94

5.2 Methodological Issues 94

5.2.1 Sample 94

5.2.2 Sampling Method 94

5.2.3 Sample Size 96

5.2.4 Self-Report Questionnaire 98

5.3 Participants' Demographic Characteristics 100

5.4 Validation of the Measurement Models 101

5.4.1 Outliers 101

5.4.2 Confirmatory Factor Analysis (CFA) 101

5.4.2(a) Malay version of the MyMAAT 102

5.4.2(b) English version of the MyMAAT 103

5.4.3 Convergent Validity With Other Instruments 106

5.4.4 Clinical Agreement 108

5.4.3 Comparison between the Malay and English versions of the MyMAAT 110

5.5 Strengths and Limitations of the Study 113

5.5.1 Strengths 113

5.5.2 Limitations 113

CHAPTER 6 CONCLUSION AND FUTURE RECOMMENDATIONS 115

6.1 Introduction 115

6.1 Research Summary 115

6.2 Implication of the Research 116

6.3 Recommendations for Future Research 117

REFERENCES 115

APPENDICES

LIST OF TABLES

Page

Table 2.1 Past research on knowledge/awareness, health perception/belief, and health-promoting behaviour/ preventive health behaviour related to medication adherence involving theories.....28

Table 3.1 Table 3.1 Summary of sample size calculation by specific objectives.....35

Table 3.2 Table 3.2 Summary of measurement tools.....41

Table 3.3 Table 3.3 Each instruments' validity and reliability used in the present study. 42

Table 3.4 Table 3.4 Statistical analyses of the present study.....45

Table 3.5 A summary of the fit indices and their respective cut-off values used in this study is shown in Table 3.5.

Table 3.5 Summary of the fit indices and cut-off value 50

Table 4.1 Table 4.1 Socio-demographic characteristics of the construct validation participants. 62

Table 4.2 Table 4.2 Summary of the item characteristics for Factor 1 64

Table 4.3 Table 4.3 Summary of the item characteristics for Factor 2 67

Table 4.4 Summary of the results from the multivariate normality test. 69

Table 4.5 Model fit indices for the Malay Version of the MyMAAT. 73

Table 4.6 Standardized factor loadings and composite reliability for initial Model-M1 74

Table 4.7 Summary of the convergent validity and construct reliability for the Model-M1 75

Table 4.8 Summary of the discriminant validity testing for the Model-M1. 77

Table 4.9 Model fit indices for the English version of the MyMAAT 81

Table 4.10 Standardized factor loadings, and reliability for initial Model-E1 82

Table 4.11 Summary of the convergent validity and the construct reliability for the Model-E1 83

Table 4.12 Summary of discriminant validity for Model-E1. 84

Table 4.13 Socio-demographic characteristics of construct validation participants. 87

Table 4.14 Crosstabulation of the adherence category based on the MyMAAT and the MMAS-8 89

Table 4.15 Correlation between the Malay version of the MyMAAT and with the Malay version of the MMAS-8. (N = 191). 90

Table 4.16 Summary of the final models from the present study 93

LIST OF FIGURES

Page

Figure 1 Illustration of the conceptual framework 30

Figure 2 Two-construct measurement model 47

Figure 3 Data Analysis Flowchartt 54

Figure 4 Q-Q plot for the Malay version of the MyMAAT 69

Figure 5 Q-Q plot for the English version of the MyMAAT 69

Figure 6 CFA path diagram for Model-M1 74

Figure 7 CFA path diagram for Model-E1 82

Figure 8 Scatter-dot plot for the Malay version of the MyMAAT and the Malay version of the MMAS-8 90

LIST OF SYMBOLS

α	Significance level
β	Statistical Power
Cp	Pooled covariance matrix for the two classes
Df	Degree of Freedom
e_{t+1}	Covariance of the errors at time, t +1
e_t	Covariance of the errors at time, t
N	Number
τ	True rating
%	Percentage
p	Significant value
ρ	Spearman's correlation coefficient
ρ_1	Expected reliability
χ^2	Chi-Square
%	Percentage
=	Equal
>	More than
<	Less than
$\geq$	More than or equal to
$\leq$	Less than or equal to
| |	Absolute value

LIST OF ABBREVIATIONS

AIC	Aikaike Information Criterion
ANOVA	Analysis of Variance
AVE	Average Variance Extracted
BIC	Bayesian Information Criterion
BMI	Body Mass Index
CDC	Centers for disease control and prevention
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CR	Composite Reliability
DOT	Directly Observed Therapy
EFA	Exploratory Factor Analysis
FDA	Food and Drug Administration
GFI	Goodness-of-fit Index
GOF	Goodness-of-fit
HbA_{1c}	Haemoglobin A1C
ICC	Intraclass Correlation Coefficient
IQR	Interquartile Range
JKWPKL&P	Jabatan Kesihatan Wilayah Persekutuan Kuala Lumpur dan Putrajaya
MARS	Medication Adherence Rating Scale
MI	Modification Indices
ML	Maximum Likelihood
MLE	Maximum Likelihood Estimation
MLR	Robust Maximum Likelihood Estimator
MMAS-8	Morisky Medication Adherence Scale-8
MOH	Ministry of Health
MyMAAT	Malaysia Medication Adherence Assessment Tool
NPV	Negative Predictive Value
PCA	Principal Component Analysis
PPV	Positive Predictive Value

PRN	When Necessary
RFID	Radio Frequency Identification
RMR	Root Mean Square Residual
RMSEA	Root Mean Squared Error of Approximation
SCT	Social-Cognitive Theory
SD	Standard Deviation
SEAMS	Self-Efficacy for Appropriate Medication Use Scale
SR	Standardized Residuals
SRMR	Standardized Root Mean Residuals
SS	Strict Stability
TLI	Tucker Lewis Index
VDOT	Video-DOT
WHO	World Health Organization

LIST OF APPENDICES

Appendix A	Study Questionnaire in Malay
Appendix B	Study Questionnaire in English
Appendix C	Original MyMAAT Scale
Appendix D	Original Malay version of the MMAS-8
Appendix E	Patient Information Sheet and Consent Form in Malay
Appendix F	Patient Information Sheet and Consent Form in English
Appendix G	Ethical Approval Letter from MREC
Appendix H	Ethical Approval Letter from JEPeM
Appendix I	Permission for using the MyMAAT
Appendix J	Permission for using the Malay version of the MMAS-8
Appendix K	Permission for using the MMAS-8
Appendix L	APPENDIX NCFA ANALYSIS USING R STUDIO FOR MYMAAT ENGLISH VERSION
Appendix M	CFA Analysis using R Studio for the Malay version of the MyMAAT
Appendix N	CFA Analysis using R Studio for the English version of the MyMAAT
Appendix O	Results of the Univariate Normality Test by Item for the Malay version of the MyMAAT
Appendix P	Results of the Univariate Normality Test by Item for the English version of the MyMAAT
Appendix Q	Results of the Bivariate Normality Test

ANALISIS FAKTOR KONFIRMATORI KE ATAS ALAT PENGUKURAN KEPATUHAN PESAKIT TERHADAP PENGAMBILAN UBAT DI MALAYSIA (MYMAAT) DALAM KALANGAN PESAKIT YANG MENGGUNAKAN UBAT KRONIK

ABSTRAK

MyMAAT telah dibentuk melalui Analisis Faktor Eksploratori (EFA) oleh kajian sebelum ini dan perlu disahkan dari aspek model pengukuran, domain, dan struktur melalui Analisis Faktor Konfirmatori (CFA). Daripada bulan Mei hingga November 2023, kajian keratan rentas ini telah dilaksanakan melalui borang soal selidik lapor diri di enam fasiliti kesihatan Jabatan Kesihatan Wilayah Persekutan Kuala Lumpur dan Putrajaya. Pesakit yang berumur≥18 tahun, dipreskrib satu jenis atau lebih ubat kronik dengan durasi minima enam bulan serta memahami Bahasa Inggeris atau Bahasa Melayu dipilih sebagai peserta kajian melalui kaedah pensampelan kuota. MyMAAT mempunyai dua peubah laten iaitu Tingkah Laku Pengambilan Ubat Spesifik (Faktor 1) dengan lapan item dan Efikasi Diri Dan Dukungan Sosial Daripada Teori Kognitif Sosial (Faktor 2) dengan empat item. Jumlah peserta adalah sebanyak 470 orang yang terdiri daripada kaum Melayu (62.7%), Cina (24.0%) dan India (12.2%). Kebanyakan peserta mempunyai lima ubat atau kurang (81.3%). Dua pembolehubah laten dan 12 indikatornya dikekalkan dalam model pengukuran akhir MyMAAT versi Bahasa Melayu dengan fit yang baik iaitu CFI=0.978, TLI=0.973, RMSEA=0.036(90%CI:0.001,0.067) dan mempunyai kebolehpercayaan yang tinggi CR=0.790 untuk Faktor 1 dan CR=0.787 untuk Faktor 2. Nilai pemuatan faktor adalah di antara 0.413 hingga 0.832 dengan p<0.001. Purata varians diekstrak untuk Faktor 1 adalah 0.664 dan Faktor 2 adalah 0.491. MyMAAT

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versi Melayu dan MMAS-8 versi Melayu mempunyai korelasi yang kuat (ρ=0.507,p<0.001) berdasarkan data daripada 191 subjek. Model pengukuran akhir MyMAAT versi Bahasa Inggeris mempunyai fit yang kurang daripada piawaian kesahan yang baik iaitu CFI=0.933, TLI=0.917, RMSEA=0.073(90%CI: 0.052,0.094) tetapi mempunyai kebolehpercayaan yang tinggi iaitu CR=0.802 untuk Faktor 1 dan CR=0.852 untuk Faktor 2. Nilai pemuatan faktor adalah di antara 0.347 hingga 0.845. Purata varians diekstrak untuk Faktor 1 adalah 0.630 dan Faktor 2 adalah 0.392. Lima puluh dua subjek menyertai uji-semula selepas lima hingga sepuluh hari dari tarikh soal selidik pertama. MyMAAT versi Bahasa Melayu menunjukkan kebolehpercayaan tahap sederhana sehingga sangat tinggi dengan ICC=0.932(95%CI:0.661,0.986) untuk Faktor 1 dan tahap rendah sehingga sangat tinggi dengan ICC=0.956(95%CI:0.325,0.997) untuk Faktor 2 melalui kaedah Model Campur Dua-Hala jenis Konsistensi. MyMAAT versi Bahasa Inggeris menunjukkan kebolehpercayaan tahap sederhana hingga sangat tinggi dengan ICC=0.911(95%CI: 0.554,0.982) untuk Faktor 1 dan tahap rendah hingga sangat tinggi dengan ICC=0.941 (95%CI:0.092,0.996) untuk Faktor 2. MyMAAT versi Bahasa Melayu mempunyai kesahan dan kebolehpercayaan untuk mengukur tahap pematuhan pesakit terhadap ubat yang baik manakala MyMAAT versi Bahasa Inggeris memerlukan penambahbaikan dan uji-kaji semula.

CONFIRMATORY FACTOR ANALYSIS OF THE MALAYSIA MEDICATION ADHERENCE ASSESSMENT TOOL (MYMAAT) AMONG PATIENTS WITH CHRONIC MEDICATIONS

ABSTRACT

The MyMAAT was developed using Exploratory Factor Analysis and the current study intends to confirm the measurement model, dimensionality and ensure the factor structure by Confirmatory Factor Analysis (CFA). A cross-sectional study was conducted using a self-report questionnaire at six health facilities in the Federal Territories Kuala Lumpur and Putrajaya Health Department between May to November 2023. Participants with age≥18 years old, prescribed with one or more chronic medications for at least six months and understand English or Malay language were selected using quota sampling. There were two constructs in the MyMAAT, namely the Specific Medication-Taking Behaviour (Factor 1) with eight items and the Social-Cognitive Theory of Self-Efficacy and Social Support (Factor 2) with four items. There were 470 participants which comprised of Malay (62.7%), Chinese (24.0%) dan Indian (12.2%). Most participants had five drugs or less (81.3%). The final model for the Malay version of the MyMAAT retained the two constructs and 12 items with good fit: CFI=0.978, TLI=0.973, RMSEA=0.036(90%CI 0.001,0.067) and with good composite reliability CR=0.790 for Factor 1 and CR=0.787 for Factor 2. The factor loadings ranged from 0.413 to 0.832 with *p*-value<0.001 The AVE for Factor 1 was 0.664 and for Factor 2 was 0.491. There was a strong correlation (ρ=0.507, $p < 0.001$) between the Malay version of the MyMAAT with the Malay version of the MMAS-8 by adherence category from the data of 191 participants. The final measurement model of the English version did not achieve the minimum level

of good fit to the data: CFI=0.933, TLI=0.917, RMSEA=0.073(90%CI 0.052,0.094) but had good composite reliability CR=0.802 for Factor 1 and CR=0.852 for Factor 2. The factor loadings ranged from 0.347 to 0.845. The AVE was 0.630 for Factor 1 and 0.392 for Factor 2. Fifty-two participants completed the test-retest after five to ten days from the first administration. The Malay version had moderate to excellent reliability based on ICC=0.932(95%CI:0.661,0.986) for Factor 1 whereas Factor 2 had poor to excellent reliability based on ICC=0.956(95%CI:0.325,0.997) by using the Two-Way Mixed Model and Consistency type. The English version had moderate to excellent reliability based on ICC=0.911(95%CI:0.554,0.982) for Factor 1 whereas Factor 2 had poor to excellent reliability based on ICC=0.941(95%CI:0.092,0.996). It can be concluded that the Malay version of the MyMAAT is valid and reliable in measuring medication adherence among participants with chronic medication(s), but the English version needs to be improved and then re-tested.

CHAPTER 1

INTRODUCTION

1.1 Background of Study

1.1.1 Epidemiology of Medication Adherence

In the year 2019, World Health Organization (WHO) published a technical report on medication safety in polypharmacy as part of the Global Patient Safety Challenge : Medication Without Harm and the highlight was that non-adherence to medication is a big issue in polypharmacy especially among the elderly or participants with multimorbidity [1]. Adherence to long-term treatment for chronic diseases in developed countries was only 50% as revealed by WHO in year 2003 and even lesser in developing countries thus making poor adherence to medication a global issue [2]. It is important to educate participants and figure out strategies to boost medication adherence rate to make sure that correct medicine to be taken at the correct time [1].

Adherence was also mentioned in another WHO report on medication safety in transitions of care due to frequent medication discrepancies between the actual medication use compared to the prescription order during new admission or discharge from healthcare facility [3]. Lack of patient adherence to medication may lead to harm by commissioned medication error for example a patient who was afraid to declare his non-adherence to the physician during hospitalization ended up getting the full dose of medication as per valid prescription subsequently developed toxicity because he has not been taking the full dose prior to admission [3].

Most publications on prevalence of non-adherence to medication in Asia were specific to a certain disease, for example a research team reviewed adherence studies specifically anti-hypertensive drug in 22 Asian countries from year 2000 to 2019 and the meta-analysis estimated the non-adherence rate was at 48% [4]. Nearly half of the

study participants were non-adherent to their antihypertensive medications, especially from the South Asia region which recorded the highest prevalence of non-adherence at 48% [4]. Among all the countries in Asia, Indonesia has the highest non-adherence rate of antihypertensive medication at 71% followed by Thailand at 69% [4]. Jordan has the lowest non-adherence rate at 15% followed by South Korea at 18% [4].

Gaynor et al. prospectively followed 150 participants with kidney transplant and found that 28 participants (18.7%) became nonadherent to the post transplantation medication therapy [5]. Adherence to immunosuppressant therapy is a significant factor in preserving the graft of an adult kidney transplant recipient [5-7]. Medication non-adherence to immunosuppressant may potentially cause serious impact to patient's health outcome as insufficient suppression of the immune system possibly led to graft rejection, graft loss, lower quality of life and even death among participants who were non-adherent to immunosuppressant medication [5,6,8].

New participants are prone to non-adherence, and it was reported that 46% of the 189 participants from a Hong Kong Hospital that were newly prescribed with 6 months antidepressant therapy, did not complete therapy with 12% discontinued their medication early within the first month [9]. In our neighboring country Singapore, a study conducted among community-dwelling elderly participants found that the level of medication adherence was poor [10]. Sixty percent of the participants were non-adherent to their therapy [10]. Insights to the medication-taking behaviour of participants are important because this information can help to identify participants who are at higher risk for non-adherence [10].

A meta-analysis of Malaysian studies up to year 2021 on medication adherence among Type 2 diabetes mellitus participants reported a low medication adherence rate of 34% [11]. Quite similarly, the prevalence of non-adherence to antihypertensive drug

was 39% in Sarawak for the year 2019 compared to 47% in Selangor for the year 2012 [12,13]. Another study done in Kuala Lumpur Hospital revealed that 55% study participants were non-adherence to anti-cancer drug imatinib for the year 2018 [14].

1.1.2 Impact of Medication Adherence

WHO published a thorough report about adherence to long-term therapies in the year 2003 to draw special attention to the magnitude and impact of poor medication adherence [2]. The lack of medication adherence diminishes the effectiveness of therapy affecting the quality of life and population health economics [2]. In year 2017, a consortium of ten organizations representing eight European countries participated in "Stimulating Innovation Management of Polypharmacy and Adherence in the Elderly" which aimed to encourage and support innovation in the management of polypharmacy and adherence in the elderly to improve medication adherence and medication safety [15]. Medication non-adherence especially in the elderly is a notable public health challenge [15]. The emphasis on adherence especially in the elderly cannot be overstated as medicine adherence is related to multimorbidity and polypharmacy [15].

It was estimated that USD$100 billion to USD$290 billion was spent in the United States, £1.25 billion in Europe and AUD$7 billion in Australia on annual health care cost related to non-adherence [14,16]. Medication non-adherence is a burden of healthcare costs because resources are wasted and underutilized [2,7,16]. Medication adherence maximizes the availability of donor organs by extending the time of a functioning graft which are precious with limited supply but endless participants on the waiting list [6,17]. Nevins et al. [8] recruited 180 participants with kidney transplant at the University of Minnesota, analysed them by their level of adherence to

immunosuppressive agent and subsequently found that there was no incident of acute organ rejection within group of best adherences.

Healthcare providers strive to lower morbidity and mortality associated with chronic diseases but frequently hampered by medication non-adherence [10]. Low adherence to beta-blocker therapy increases the risk of coronary heart disease complication by 4.5 times [18]. Poor adherence to asthma medication among the moderate-to-severe asthmatic geriatric participants increases the risk of hospitalization by 20% [19]. Patients who greatly adhere to drug therapy have better outcome and better quality of life compared to patient who are not [5,14,20]. Non-adherence to immunosuppressant therapy after renal transplant was associated with graft loss later on in life [8]. This was supported by a meta-analysis of ten cohort studies showing that the odds of graft failure were sevenfold higher in nonadherent participants versus adherent participants [6].

Medication non-adherence heightens the likelihood of relapse, drug resistance and treatment failure therefore reduce survival rate [2]. Non-adherence to antidepressant treatment has been identified as a significant factor for an eightfold increment in the odds of relapse or recurrence of depressive episode within one year from therapy commencement among psychiatric participants in a Hong Kong hospital [9]. The importance of reliable evaluation of adherence behaviour is to ensure that changes in health outcomes correspond with the prescribed regimen for better planning and effective treatment [21]. Population health outcomes based on treatment efficacy data may be lower than expected when adherence rate is not taken into consideration [2].

1.1.3 Importance of Non-Adherence Identification

Patients scored their medication adherence higher than the true scores due to the stigma of being labelled as non-adherence [17]. Simmons et al. [22] concentrated on finding out the truthfulness in self-report adherence using electronic nebulizer chronologs, a device that records the timing of inhaler actuation, and the result was shocking. Thirty out of 101 participants (29.7%) who were all unaware of the function of the recorder, committed to once or more "dose dumping" throughout the first year. "Dose dumping" was defined as any episode of ≥ 100 actuations within 3 hours period [22]. Intentional dumping of study drug was done to give the impression of good adherence to study protocol [22].

It is particularly important to be able to detect if drug non-adherence is presence among the participants in disease prevention and clinical trials of new agents or new regimens because it attenuates the relationship between therapy and the dependent variable [8,22,23]. Without credible adherence data, it is impossible for clinical research to get accurate findings because a null result may not be due to poor drug efficacy but substandard adherence [23]. In other words, it is more difficult to prove that there is a significant difference in outcome if non-adherent participants are included in the study thus increasing the size of "intend to treat" trials [8,22].

The ability to identify participants who have the likelihood of being non-adherent to medication facilitates the process of deciding which patient to target for adherence promotion [24]. Personalised adherence-enhancing interventions rely heavily on the recognition of individual non-adherence and its factors [24,25]. Knowing a patient belongs to which category of adherence makes it easier to devise a treatment plan to reach realistic goals related to their health outcome [2].

According to a systematic review published in year 2019 on adherence interventions, participants who had poor medication adherence improved following patient education or counselling [26]. It was shown that with patient education, the morbidity was lower whereas patient satisfaction was higher [26]. A recent systematic review concluded that patient adherence to chronic obstructive pulmonary disease (COPD) drug therapy increased with educational and extensive verbal instruction and motivational interviews delivered by the healthcare provider [27]. These efforts lowered the number of hospital admissions [27].

The ability to accurately categorize a patient into good or poor adherence group helps healthcare providers to focus the right effort and resources on their target group. Asthmatic participants with unsatisfactory baseline medication adherence were shown to have clinically significant improvement in adherence resulting from digital interventions such as electronic monitoring devices for example electronic drug bottles that can beep and blink as a reminder to user to consume medication [28] and short message services [29].

Nevertheless, adherence issue remains a persistent issue globally until today because there has been an inclination to concentrate on a single factor at a time which is expected to have limited effectiveness [2]. Multilevel targeting on more than one determinant using more than one approach is recommended by WHO since there is not one intervention that can be effective for all the different types of participants in various settings [2].

To curb non-adherence among participants is still an ongoing effort and there is no one-size-fits-all approach in addressing this issue covering all participants regardless of conditions or setting [2]. Accessibility to training in adherence management is important to healthcare professionals to improve their skills in

assessing participants for non-adherence and performing timely interventions [2]. Besides that, family and community support may influence patient adherence to medication at home [2].

1.2 Problem Statement

In Malaysia, patient adherence to medication assessment is often done by pharmacists. Before the year 2015, pharmacists working in the facilities Ministry of Health (MOH) were using the Morisky Medication Adherence Scale (MMAS) of the Malaysian version for free. At the time of writing, the cost of the MMAS-8 license starts at USD$6000 for up to 1000 administrations [30]. From 2015 onwards, employees of MOH were discouraged from using the MMAS-8 as it was no longer a cost-effective method to assess medication adherence due to the expensive fee imposed on its usage.[21]

There was no standardized medication adherence assessment tool being used in MOH facilities. Healthcare practitioners including pharmacists were using their own judgment to evaluate patients since the discontinuation of MMAS-8 usage in MOH facilities. A validated, reliable, and cost-effective tool for the measurement of medication adherence is much needed because the assessment outcome varies between raters when there is no standard tool available.

1.3 Justification of Study

Hatah et al. developed the Malaysia Medication Adherence Assessment Tool (MyMAAT) for patients on the anti-diabetic drug(s) through Exploratory Factor Analysis (EFA) in year 2020 and this self-report questionnaire is a promising and inexpensive tool to replace MMAS-8 for use in MOH facilities [21]. It was demonstrated that the MyMAAT had acceptable internal consistency of Cronbach's

alpha = 0.910 and test-retest reliability using ICC resulted in ρ = 0.96 (95%CI 0.93 to 0.98, p =0.001) [21].

The MyMAAT items were first prepared in Malay language and then translated to English using the forward-backward method [21]. The items were then combined into a bilingual questionnaire and EFA was done on the bilingual MyMAAT [21]. Questionnaires translated into different languages may and may not exhibit the same characteristics such as sensitivity and specificity. For example, MMAS-8 in the Malay language has a sensitivity of 77.61% and specificity of 45.37% using HbA_{1c} compared to the Korean language sensitivity of 74.1% and specificity of 38.3% [31,32]. The EFA done on the MMAS-8 Persian version found two-construct structure while the Thai version has three-factors structure [33,34].

The measurement theory obtained from the EFA for the MyMAAT has not been confirmed through Confirmatory Factor Analysis (CFA). It is important to confirm the measurement model based on the EFA finding to ensure the factor structure and to confirm the dimensionality of the MyMAAT [35]. The MyMAAT was developed by studying adherence to anti-diabetic drug(s) only [21]. In order to be useful for nationwide use in Malaysia whereby patients are on multi-medications ranging from anti-hypertensive drugs to anti-cholesterol drugs, it is crucial to study the validity and reliability of this tool in patients on all type of chronic medications to mimic the real practice.

1.4 Significance of Study

CFA is an extension of EFA to confirm theory set forth by the previous study [21,35]. Goodness-of-fit tests are necessary to evaluate the hypothetical model [35]. EFA is used to refine the MyMAAT by reducing the number of original items by

retaining items with appropriately high loading factors while CFA allows the testing of the factor structure or dimensionality of the MyMAAT [35]. The MyMAAT is easy to use and inexpensive which is the best option to be standardized as a medication adherence assessment tool to be used national wide in healthcare facilities. The MyMAAT can be used to identify the cause of non-adherence among patients with long-term medication thus facilitate healthcare provider in addressing the issue of non-adherence [36]. The MyMAAT can also be used multiple times to gain insights to the adherence trend in a patient as adherence level may vary over time.

1.5 Research Questions

1. Is MyMAAT a valid and reliable self-reported questionnaire for medication adherence assessment among patients with chronic medication(s)?
2. What is the construct validity and composite reliability of the Malay and English versions of the MyMAAT using the CFA?
3. Does the Malay version of the MyMAAT correlate with the Malay version of the MMAS-8?
4. Is he Malay and English versions of the MyMAAT stable over time?

1.6 Research Objectives

1.6.1 General Objective

The objective of this study is to validate the Malay and English versions of the MyMAAT in measuring medication adherence among patients with chronic medication(s).

1.6.2 Specific Objectives

1. To determine the construct validity and composite reliability of the Malay and English versions of the MyMAAT using the CFA.

2. To determine the correlation between the Malay version of the MyMAAT and the Malay version of the MMAS-8.

3. To determine the stability of the Malay and English versions of the MyMAAT over time by test-retest reliability.

1.7 Research Hypothesis

1. The Malay and English versions of the MyMAAT are valid and reliable using the CFA.

2. There is a correlation between the Malay version of the MyMAAT and the Malay version of the MMAS-8.

3. The Malay and English versions of the MyMAAT are stable over time by test-retest reliability.

CHAPTER 2

LITERATURE REVIEW

2.1 Chronic Medication

2.1.1 Definitions

In the literature, the definition of chronic medication varies in terms of duration. One way of defining chronic medication is prescription medication or over-the-counter medication for chronic disease taken daily for at least three months [37-39]. Others specify at a duration of at least 30 days [40,41] and another one interprets the frequency and duration as taken when necessary but with an expected duration of at least 30 days cumulatively within six months [40].

According to the CDC, chronic diseases are health conditions that persist for at least one year with the need for continuous medical service or restricted daily activity or both [42]. Examples of chronic diseases are hypertension, coronary heart disease, diabetes, dyslipidaemia, and arthritis [42].

2.1.2 Epidemiology of Chronic Diseases

In the United States, six out of ten adults have a chronic disease, and four out of ten adults have two or more diseases. Chronic and mental health conditions accounted for a whopping 90% of the United States $4.1 trillion annual health care expenditure [42]. The mortality rate for heart diseases and stroke are high and contributed a third of all deaths in the United States [42].

Half of the top ten principal causes of death in year 2021 in Malaysia are chronic diseases namely the ischaemic heart diseases, cerebrovascular diseases, diabetes mellitus, hypertensive diseases, and chronic lower respiratory diseases [43]. During the pre-COVID 19 era, ischaemic heart diseases used to be the largest contributor to

mortality both in the year of 2017 and year of 2018 with cerebrovascular disease and chronic lower respiratory diseases at the top five causes of death [44].

Citizens more than 60 years old utilize about 50% of all the prescription medication and 60% of the medication-related cost in spite of making up only 12% to 18% of the total population in developed countries [2].

2.2 Medication Adherence

2.2.1 Definition

WHO defined medication adherence as the extent to which the use of medication by the patient agrees with the prescribed regimen [42].

2.2.2 Type

Intentional non-adherence is a deliberate choice to not use the medication as instructed by a healthcare provider while unintentional non-adherence is the failure to remember to use the medication as prescribed [45]. In the Jackson Heart Study on patients with one or more chronic diseases, there were more patients who identified themselves as both intentional and unintentional non-adherence to medications as compared to the patients who saw themselves as either one [45]. A pilot study in Poland analysed the responses of 41 elderly patients and found that patients who intentionally did not adhere to the prescription by changing the drug dose, omitting a dose or self-discontinuation of the drug without consultation while those who unintentionally did not adhere to the prescription, did so by failing to remember a dose or overlooking on a dose [46].

Apart from this, Dunn et al. [17] identified overt non-adherence as the behaviour of openly admitting the action of not taking medication as prescribed for an extended duration. Patients may have less than ideal adherence level subtly or overtly and it may

happen sporadically or continuously throughout their treatment duration [17]. Non-adherence covers various medication-taking behaviours from neglecting a dose, wrong dose to wrong timing of medication administration which can be caused by insufficient direction by healthcare professionals, lack of knowledge regarding the correct way of medication usage and inability to acquire the prescribed medication due to financial constraints [7]. A lesser explored type of adherence is over-adherence where patients take more doses than they should [47].

Another form of non-adherence is erratic non-adherence which is described as forgetfulness and living a hectic daily life [2]. These patients have a good understanding of their regimen and would like to adhere but find it hard to comply due to life complexity and not prioritizing the treatment plan [2]. An example of this situation is a patient practising good adherence on weekdays with disruption to their medication routine over weekends or holidays [2]. Albeit not a popular term in Malaysia, unwitting non-adherence is expressed as misinterpretation or insufficient understanding of the regimen prescribed by the physician or the necessity for adherence [2]. To elucidate this, some patients are confused between PRN medication with daily medication [2]. Another example is the patient misunderstood medication that was prescribed for 'daily use' as 'daily use when there is symptom' and vice-versa [2].

An additional group of non-adherence is the intelligent non-adherence which constitutes of patients who purposely change their regimen by making a reasoned choice, which does not necessarily mean a wise choice. These patients may discontinue their therapy when they are sufficiently convinced that the disadvantages of therapy exceed the advantages [2]. In the management of diseases, a good understanding of the variation and complexity of patient non-adherence is of utmost importance [2]. Some patients may exhibit different medication-taking behaviour for each drug that they are

prescribed, for example, a patient may be unintentionally non-adherence to one drug and intelligent non-adherence for another drug which goes to say there is not a one-size-fits-all solution for non-adherence [48]. Having said that, recognizing the type of non-adherence is essentially the key to addressing this issue [49].

2.2.3 Measurement Tool

There is no gold standard for medication adherence monitoring [50,51]. There are objective and subjective, direct, and indirect, invasive, and non-invasive method of measuring medication adherence [23,25,50]. Direct methods are more accurate but are more expensive [25,50]. Questionnaires, self-reports, pill counts, prescription refills, electronic drug bottle caps, assessment of clinical response and measurement of physiologic markers are examples of indirect methods. On the other hand, ingestible sensor, serum drug level, urine drug level and directly observed therapy (DOT) are direct methods [23,25,50].

Examples of objective approach are the measurement of level of drug in the blood, the measurement of biological marker in the blood, pill counts, and prescription refills while the subjective approach encompasses the healthcare provider's evaluation of patient's medication-taking behaviour [25,52]. The newer technology involving ingestible sensors is deemed as invasive compared to non-invasive methods like questionnaires, pill counts and electronic drug bottle caps.

2.2.3(a) Traditional

Patients' serum drug concentration and urine drug metabolite level data are direct, objective, and quantitative measurements of adherence as the drug level is influenced by the amount of drug intake [7]. Patients with poor medication adherence were more likely to have subtherapeutic serum levels of drug [7]. Serum drug level needs blood withdrawal, which is invasive, expensive reagents and susceptible to

patient-factor such as timing of drug ingestion and sampling time [7]. Patient may heighten their medication adherence as the time gets closer to the day of blood withdrawal thus examining serum drug level at only a single point has little information on the overall medication adherence and should be interpreted as a trend or together with another marker [7,8].

The source of information pertaining to adherence affects the accuracy of the measurement [7]. Self-report using questionnaires depends on the recollection of past medication behaviour which may not be a reliable source of information [8,23]. Some studies measure adherence indirectly by checking on the patient's medication refill records from the pharmacy which is made easier if the pharmacy has computerized system for prescribing and dispensing [7]. Refill data from the pharmacy is an objective measure but it does not consider events where patients refill their medication at other pharmacies [7]. And though refill data showed that the medication had been collected but without direct observation, it is not proven that the patient had administered the medication according to the prescription [7].

DOT has long been implemented in Malaysia, especially for anti-tuberculosis drugs [53] and this method can be taken up a notch and expanded for various other drugs through Video-DOT (VDOT) that can be done in two ways, either the drug administration is observed by a live video call session between patient and healthcare provider or video recording of the session by the patient which is then reviewed by the healthcare provider [54]. Technology has brought a change of scene to adherence measurement and monitoring. Compared to the traditional way of adherence monitoring by DOT, VDOT offers more flexibility and convenience to patients as they can be monitored at the comfort of their home with the advantage of real-time monitoring [54].

2.2.3(b) New Technology

In the international healthcare arena, electronic monitoring is said to be the most accurate [6] method in measuring adherence quantitatively [8] and is widely used in studies abroad but it is not common in Malaysia. A recent study by Mason et al. [54] reviewed 79 articles on medication adherence using monitoring technology of various functions which can be further grouped to electronic drug containers, blister packet technology, ingestible medical devices, electronic medication management systems, patient self-report–based technology, video-based technology, and motion sensor technology.

Two common designs available in the global market are electronic monitors sealed in drug bottle caps or on the blister pack, with the intention to capture the time of each cap opening or blister package tearing that serves as a proxy for medication intake [8,54]. To get more accurate record of events, the concept of a singular blister pack with just the right amount of drug for peruse reduces the possibility of over or under-dosing and also curiosity opening which is opening a device without any medication removal [54].

Medication Behaviour Monitoring System is particularly useful for patients with multiple drugs, multi-dosing, or complex regimens because the drug, dose, frequency, and timing are pre-set with a dispensing mechanism [54]. Most technologies do not guarantee the consumption of the medication, hence the invention of an ingestible sensor which can even detect numerous ingestions at the same time [54]. This invasive method monitor adherence by using digital pills which is a combination of drug-device. When a patient consumes the digital pill, the sensor within the pill will be activated when in contact with stomach gastric juice and the time of ingestion will be detected by an external monitor [54]. On top of that, there are devices that employ a Medication

Behaviour Monitoring System which integrates a reminder alarm, motion sensor of the arm-raising-to-drink-water action, drug dispenser on a scale platform and recorder of the changes in the scale when the drug is lifted, and the scale goes back to zero [55].

Real-time monitoring enables healthcare providers to have access to the data related to patient's medication adherence immediately by wireless transmission. VDOT, electronic drug bottle, and electronic medication management systems apply this concept [54]. An electronic medication management system can be elucidated by a medication adherence intelligence system that produces audio reminders at the same time rotates the right drug bottle by utilizing a radio frequency identification (RFID) based tag [54,55]. When the drug has been removed, the scale measures the weight of the bottle to calculate the number of doses taken out. Another device releases the drug only at the planned time, planned dose, and right into the user's mouth [50].

Although researchers conceived more ideas and developed new devices to measure and improve adherence, most of them are still a proxy measure for medication adherence. The electronic cap bottle, electronic blister pack and electronic medication behaviour system are just an estimate of medication adherence and by no means confirm the actual use of the medication as prescribed [54]. Whilst the ingestible sensor tracks the medication to the point of ingestion, it is not without risk considering its invasive nature. There were reports of mild skin rashes [56,57] and nausea [56] and diarrhoea [57]. Theoretically, it is possible for the retention of the tag [23] and a change in drug dissolution [23]. Other limitations of using technology are the limits of the design itself and the inconsistency of the device use. The act of tearing a blister pack dose may affect the conductive track of other doses causing accidental signals to be recorded [58]. Technical issues may arise and cause failure of recording for example poor video quality in VDOT, faulty parts of electronic devices, and battery failure [22,59].

The ideal method should be straightforward, easy, accurate and economical with the ability to include information about the trend, belief, and hindrance to adherence but unfortunately, this perfect method does not exist [52]. Each approach has its own advantages and disadvantages based on the context of its use and hence, it is best to combine at least two methods [52].

2.2.4 Scoring

The two most popular ways of scoring adherence levels are by taking the percentage of days that a patient took the correct dose in a month and the percentage of doses taken correctly per day for multiple dosing medication [47]. There is no standardized cut-off point to differentiate adherence from non-adherence, the range is between 5% to 33% but most studies set non-adherence as missing 20% or more doses [47]. To illustrate this, the number of medication doses filled by the pharmacy is compared to the number of doses prescribed by the physician and the resulting compliance rate of $\geqslant$80% is considered as being adherent to the treatment [7].

The basis of adherence classification ideally should be clinical based whereby the cut-off point for adherence score should potentially bring a meaningful impact to the clinical setting [47]. Another view would be having a threshold value based on individual drugs rather than a blanket number, suggesting that pharmacokinetic and pharmacodynamic characteristics of the drug are to be considered as well [47]. For instance, missing 3% of the daily dose of an immunosuppressive agent was reported to increase the risk of organ rejection post heart transplantation by De Geest et al. [60].

Additionally, another measure of adherence is classifying non-adherence as deviation from the prescribed dosing time which several studies fixed it between two to four hours [47]. Different studies measure non-adherence differently but in general, the conclusion is based on the number of doses not taken or modified by the patient whether

due to a missed dose, forgotten dose or adjusted dose [6]. It is challenging for retrospective, prospective, and interventional research because the degree of non-adherence that is associated with inferior results is not yet established, and it varies from disease to disease [17].

2.2.5 Factors

The ability to identify potential adherence barriers is a step towards the elimination of the barrier [24].

2.2.5(a) Social and Economy

Ethnic

The literature showed varied results for adherence scores based on ethnicity. Ramli et al. and Asiri et al. showed that adherence is correlated with ethnic groups but Thew et al., Osterberg et.al. and Ahmad et al showed no significant difference between the ethnic groups in terms of adherence level [12,13,25,61,62]. A Malaysian study found that Indian patients were less likely to adhere to medication prescribed by physician than Malay and Chinese patients [13]. Several international reports on medication non-adherence showed higher probability in non-white patients [61,62].

Age

A wide range of conclusion were drawn on the relationship between age and medication adherence. It was reported that adherence level decreased with age [13]. In contrast to that study, Thew et al., Mentz et al, Ahmad et al. and Plaza et al. found that the younger patients were more likely to be non-adherent to medication [12,45,62,63]. Junaid et al. and Kan et al. found that there was no association between adherence and age [20,64].

Gender

There was a diverse outcome regarding the relationship between gender and medication adherence in the literature. Thew et al., Junaid et al., Ahmad et al. and Tabyshova et al. reported that gender did not influence the adherence level [12,20,62,65]. On the contrary, Ramli et al. and Schoberberger et al. found that female patients were more adherent than male patients [13,66]. Jackson Heart Study contradicted the studies above with the findings of more intentional non-adherence among female patients and the overall rate of non-adherence in females was slightly higher than in male [45].

Education

The influence of education level towards medication adherence were examined by previous studies and resulted in varied findings. According to Schroeder et al., illiteracy and low level of education were the factors of non-adherence to medication [2]. Conversely, patients with tertiary education were also more likely to be non-adherence to medication based on Thew et al. and Boima et al.but opposed by a systematic review done by Gast et al [12,24,67]. Apart from that, Ahmad et al. found that there was no significant difference between the level of education and medication adherence [62].

Employment

Patients who were pensioners or had retired demonstrated better adherence [12]. Unemployment contributed to lower adherence to medication according to Schroeder et al. but Tabyshova et al. showed no significant difference between employment and adherence levels [2,65]. Having a job showed a positive effect on adherence to oral regimen in adult patients with chronic diseases although the impact was uncertain

according to an overview on systematic reviews of medication adherence [24]. This conclusion is contradicted by Plaza et al. which related working status with non-adherence [63]

Income

Patients who had lower income were associated with lower adherence than those who had higher income range [2,24]. Thew et al. and Tabyshova et al. suggested that there was no significant correlation between adherence to medication and monthly household income.

2.2.5(b) Therapy-related Factor

Patients with comorbidities, complex medical regimens or with frequent modification to treatment were found to be less adherent to medication [2,20,25,62]. Besides that, the number of medications prescribed varied inversely with the level of adherence [13,20,42,68]. Patients taking more than three types of medication were found to be only 50% adherence to medication [15]. However, Ahmad et al. found that there was no significant difference between the two variables [62]. A simpler regimen promoted adherence to medication whereas a regimen with a four-times-a-day dosing raised the non-adherence rate [25]. Tabyshova et al. contradicted that by demonstrating no significant difference between the frequency of medication with adherence level [65].

Those patients who experienced side effects from taking a medication also tend have poor adherence to medication [2,20]. A research conducted in Singapore found that the assessment of treatment satisfaction which included the examination of the side effects, effectiveness, and convenience of the prescribed regimens to the patients, was the key to boosting medication adherence particularly among the older community with chronic diseases [10].

2.2.5(c) Patient-related Factor

Patient-related factor is described as the means, comprehension, awareness, attitude, faith, impression, insight, and expectation of the disease, symptoms, possible complication, and improvement on medication [2].

To illustrate this, Chisholm et al. found that patients who were given free medication adhere to their drug regimens initially, but the adherence level consistently declined with time [7]. Generally, patients display good adherence at the start of the treatment probably due to more appointments, but the discipline drained out over time. It was reasoned that patients were excited in the beginning but slowly became "more comfortable with their condition" and maybe "more willing" to stray off the planned therapies [7].

Some studies [20,25] found that patients had poor adherence due to forgetfulness, away from home, difficulty in taking medicine, lack of information, self-decide to omit doses, and self-discontinue medication when they felt that their health improved. Elderly patients were more prone to diminished cognitive and physical functions thus the risk of poor adherence was augmented [2]. This was especially true in multi-medication regimens because the inclination to forget and skip doses was higher [20,68].

2.3 Medication Adherence Questionnaires

2.3.1 MyMAAT [21]

The MyMAAT is a self-report questionnaire that is inexpensive and favourable in a busy clinical setting for a population that has moderate to good reading proficiency. Initially, there were 21 items with five-point Likert-scale responses to enable respondents to demonstrate their level of agreement or disagreement with each

statement related to their adherence. There were six constructs and they comprised of medication-taking behaviour, perceived utility (benefits, costs, and efficacy), perceived barriers, others, Social-Cognitive Theory (Self-Efficacy and Social Support.), perceived severity and susceptibility. Hatah et al. developed the Malaysia Medication Adherence Assessment Tool (MyMAAT) for diabetic patients through a literature review of earlier validated medication adherence evaluation tools.

One of them was a systematic review done by Nguyen et al. [69] on 43 validated English versions of self-report questionnaires related to medication adherence. It was identified that adherence scales usually intend to extract one or more of the following information namely the patient medication-taking behaviour, barriers to medication adherence and beliefs associated to adherence [69]. It was concluded that the self-report questionnaires had the prospect of measuring both medication-taking behaviour and/or pinpointing hindrances to adherence and beliefs related to adherence [69].

Not only that, Hatah et al. based their research on a local study on medication adherence between subsidized and self-paying patient to see patient's motivation when cost was and was not involved [70]. This study reported that the demographic factors such as age, gender, monthly income, education level, marital status, patient residing location, frequency of medication, number of health problems and number of medications prescribed, and payment scheme were not significant factors towards medication adherence among the study patients [70]. Only attendance of drug counselling session increased the adherence rate by three times (adjusted odds ratio of 3.29, 95% CI was 1.42 to 7.62, $p = 0.006$) [70].

Furthermore, a systematic review on health psychology theories of behavioural changes that pivoted around medication adherence was referred and incorporated during the development of the MyMAAT [71]. The objective of this review was to provide

empirical evidence in the context of three theoretical frameworks which were the Social-Cognitive Theory, Self-Regulation Model, and the Social Support Theory [71]. This review of 67 articles highlighted five health-related behaviours that were significant predictors of adherence, and they were self-efficacy, perceived barriers, perceived susceptibility, necessity beliefs and medication concerns [71].

The final MyMAAT consists of 12 items with two factors namely the Specific Medication-Taking Behaviour and Social-Cognitive Theory of Self-Efficacy and Social Support. that explain the total variance of 61.76%. Item number 1 to item number 8 load on Factor 1 with cumulative variance explained 52.06% whereas item number 9 to item number 12 load on Factor 2 with cumulative variance explained 9.69%. The final items had excellent internal consistency with Cronbach's alpha = 0.91. Item-total correlation coefficients were between 0.52 to 0.72 showing moderate to strong correlations of all 12 items to the total scale. Inter-item correlation coefficients were between 0.26 to 0.73 showing moderate to strong correlations of the 12 items.

2.3.2 Malay version of the MMAS-8 [31,51,72]

Malay version of the MMAS-8 is a validated translated questionnaire among diabetic patients in Malaysia. According to Al-Qazaz et al. there was a significant correlation between adherence and education level but there was no association between age, sex, BMI, race, employment, number of medication and duration of diabetes with the adherence. Most of the responses to the questions in the Malay version of the MMAS-8 are dichotomous (Yes/No). The correlation between HbA_{1c} group with adherence score was significant implying that the Malay version of the MMAS-8 is a valid instrument which can differentiate patient clinically by their glycaemic control.