STUDY PROTOCOL

Study Protocol of a Mixed-Methods Study to Develop and Validate the Malaysian Anti-Hypertensive Agents Non-Adherence Scale in Hypertensive Patients

Sheng-Qian Yew[1], Ahmad Iqmer Nashriq Bin Mohd Nazan[1], Kit-Aun Tan[2]

[1] Department of Community Health, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia
[2] Department of Psychiatry, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia

ABSTRACT

Introduction: Domains of adherence and non-adherence to hypertensive medications have not been extensively documented in Malaysia due to the absence of theoretically driven and culturally appropriate measurement tools, leading to a poor understanding of the adherence and underlying factors. We aim to identify these domains in Malaysian hypertensive patients and subsequently apply the findings to develop and validate the Malaysian Anti-Hypertensive Agents Non-Adherence Scale (MAANS). **Methods:** This study has an exploratory mixed-methods design. In Phase 1, we will recruit hypertensive patients from two health clinics to participate in a semi-structured interview. Recruitment of participants will terminate once thematic saturation is achieved. Coding and thematic analyses will be performed to identify the domains of adherence and non-adherence to anti-hypertensive medications. In Phase 2, based on the domains generated from Phase 1, we will develop the Malaysian Anti-Hypertensive Agents Non-Adherence Scale (MAANS). Four hundred hypertensive patients will be randomly selected. Data from 200 participants (serving as the calibration sample) will be subjected to exploratory factor analysis while data from additional 200 participants (serving as the validation sample) will be subjected to confirmatory factor analysis. Factor structure, predictive validity, and reliability of the MAANS will be statistically tested. **Discussion:** With the presence of the MAANS, health care providers can gather crucial information regarding barriers and facilitators to hypertensive treatment adherence and design effective health promotion programmes to reduce complications of uncontrolled hypertension. **Trial registration:** Ethical approval is granted by the Medical Research Ethics Committee, Ministry of Health, Malaysia (NMRR-18-3251-44694).
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Corresponding Author:
Ahmad Iqmer Nashriq Bin Mohd Nazan, PhD
Email: iqmernashriq@upm.edu.my
Tel: +603-9769 2941

INTRODUCTION

Hypertension is an increasingly important public health issue with a global prevalence of 31.1% (1). In 2019, the prevalence of hypertension was 30.0% among the Malaysian population (2). Moreover, the number of adults with hypertension in 2025 is predicted to increase by about 1.56 billion globally (3). Such increase is owing to the issues of ageing as well unhealthy and sedentary lifestyles (4). However, there is insufficient blood pressure control in hypertensive patients, although anti-hypertensive drugs are highly available (5, 6).

In developed countries, adherence to medication among patients with chronic diseases averages only around 50% (7). Meanwhile, in Malaysia, the data on medication adherence are scarce. To date, only a small number of medication adherence studies are available in Malaysia. In one study, Ramli et al. reported that only 53.4% of patients had adhered to the prescribed hypertensive medications and the control of hypertension was far beyond satisfactory (8). Furthermore, in 2020 that 25% of hypertensive patients in Malaysia had poor adherence to their hypertensive medications (9). These statistics are alarming and should serve as a wake-up call for research into non-adherence with anti-hypertensive drugs.

Therefore, the domains of adherence and non-adherence to hypertensive treatment warrant scientific investigations. Many researchers have attempted to develop scales for measuring adherence to anti-hypertensive treatments. These scales include but are not limited to nine-item Brief Medication Questionnaire

(BMQ) (10), four-item Morisky Medication Adherence Scale (MMAS-4) (11), eight-item Morisky Medication Adherence Scale (MMAS-8) (12), 25-item Maastricht Utrecht Adherence in Hypertension (MUAH-25) (13), 16-item Maastricht Utrecht Adherence in Hypertension (MUAH-16) (14), 28-item Treatment Adherence Questionnaire for Patients with Hypertension (TAQPH) (15), 14-item Hill-Bone Compliance Scale (HBSC) (16), and seven-item Self-Efficacy for Appropriate Medication Use Scale (SEAMS) (17). The characteristics and psychometric properties of these hypertensive-related questionnaires are illustrated in Table I.

The BMQ, MMAS-4, MMAS-89, HBSC, and SEAMS were developed from a quantitative approach, whereas MUAH-16 and MUAH-25 were developed using a qualitative approach. Only the TAQPH was developed from a mixed-methods approach. As far as theoretical framework is concerned, only the SEAMS can trace its roots back to Bandura's Social Cognitive Theory (17). The use of a conceptual framework in the development of the remaining scales was unclear.

Drug adherence is a multidimensional construct encompassing patient- (e.g., MUAH-16, MUAH-25 and TAQPH), health system- (e.g., MUAH-16 and MUAH-25), therapy- (e.g., MUAH-16, MUAH-25, and TAQPH), and condition-related factors (e.g., SEAMS) (18). In particular, the MUAH-16 (14), MUAH-25 (13), TAQPH (15), and SEAMS (17) are multidimensional, whereas the MMAS-4 (11), MMAS-8 (12), and HBCS (16) are unidimensional. Often, patients are just classified as adherent or non-adherent to drug therapy. However, if the domains for their adherence and non-adherence were better understood via a multidimensional scale, intervention programs to improve drug adherence could be more optimised and thus more successful. In addition, utilising a multidimensional scale may prevent considerable loss of information as seen in unidimensional scales (19).

Health care utilisation can vary across different countries and cultures. For example, the self-reported MMAS-8 has been widely used to assess drug adherence in hypertensive patients, thanks to its broad validation and translation studies and outstanding validity and reliability properties (20). However, other hypertension-related scales have not been validated outside the setting in which they were initially developed. One such example is HBCS. The scale was developed and validated in an African American community (21) and appeared to have better performance in African than non-African populations (22). Therefore, this scale is suggested for studies measuring hypertension in a predominantly African population.

Psychometric properties of a scale can be assessed through reliability and validity. It has been suggested that a Cronbach's alpha of at least .70 is required to indicate adequate internal consistency (23). Based on such standards, MMAS-4 (11) and MUAH-16 (14) fail to demonstrate acceptable internal consistency. Some scales have shown satisfactory reliability in the original scale development studies, but they did not perform well psychometrically when used in patients residing in different countries. MMAS-8 was translated into French (24) and Urdu (25) versions. The Cronbach's alphas were .83 for the original version, .54 for the French version, and .71 for the Urdu version. When taking the validity of the scales into account, only HBCS (16) and TAQPH (15) reported evidence for content validity. Only MUAH-16 (14) and MUAH-25 (13) have documented evidence for convergent validity, whereas MMAS-4, MMAS-8, TAQPH, and SEAMS have documented evidence for criterion-related validity. No construct validity information is yet available for BMQ (10).

No single measure that can be appropriately administered in the context of Malaysian hypertensive patients is available. Some existing scales are unidimensional (e.g., MMAS-4, MMAS-8, and HBCS) and have low reliability and validity estimates (e.g., MMAS-4 and MUAH-16). Other scales are not built upon a solid conceptual framework (e.g., BMQ, MMAS-4, MMAS-8, MUAH-16, MUAH-25, HBCS, and TAQPH) and are culturally specific (e.g., HBCS). Therefore, there is a timely need to develop a theoretically driven, multidimensional, reliable, and valid scale for assessing the domains of adherence and non-adherence to anti-hypertensive medications in Malaysia. Hence, the objective of the present study is to identify themes of adherence and non-adherence to anti-hypertensive medications in hypertensive patients (Phase 1) and to develop and validate the Malaysian Anti-Hypertensive Agents Non-Adherence Scale (MAANS) (Phase 2). This study has an exploratory mixed-methods design and will be conducted from June 2021 to December 2021.

METHODS

PHASE 1

In Phase 1, we will use a qualitative approach to identify the domains of adherence and non-adherence to anti-hypertensive drugs in hypertensive patients.

Study Participants

For Phase 1, data collection and participant recruitment will take place at health clinics located in Kuala Lumpur. Although there are 13 health clinics in Kuala Lumpur, only two clinics will be randomly selected. Purposeful sampling will be conducted to select eligible hypertensive patients attending the participating health clinics from June 2021 to December 2021. We will identify the hypertensive patients from the patients' registry. Potential participants will be reached through phone calls, subject to the inclusion and exclusion criteria listed below. The interview session will include

Table I: Hypertension-related questionnaires

Questionnaires	Country of Origins	Indications	Number of Items	Aims	Reliability	Validity	Settings	Developed Upon Theoretical Framework
Brief Medication Questionnaire (BMQ)	• United States	• Multiple chronic diseases including hypertension	• Consists of three subscales with nine items	• To assess patient's medication-taking behaviour, barriers to adherence, and beliefs about drug efficacy	• Not reported	• Not reported	• Local pharmacies	• No
Four-item Morisky Medication Adherence Scale (MMAS-4)	• United States	• Hypertension	• Consists of four dichotomous items	• To identify barriers to medication taking	• Internal consistency: Cronbach's alpha = .61	• Criterion-related validity: Individuals who scored high on the MMAS-4 were significantly more likely to have their blood pressure under control • Construct validity: EFA indicated that the eight-item loaded well on a single factor	• Outpatient clinic in a hospital	• No
Eight-item Morisky Medication Adherence Scale (MMAS-8)	• United States	• Multiple chronic diseases including hypertension	• Consists of eight items. The first seven items are dichotomous responses while the last item is a five-point Likert response	• To identify barriers to drug adherence especially attitudinal and behavioural problems • To monitor adherence level over the course of the treatment	• Internal consistency: • Cronbach's alpha = .83	• Criterion-related validity: MMAS-8 score is significantly correlated with that of the MMAS-4, where Pearson's correlation = .64; p<.05) • Construct validity: CFA indicated that the eight-item loaded well on a single factor	• Hospital	• No
Maastricht Utrecht Adherence in Hypertension (MUAH)-25	• Netherlands	• Hypertension	• Consists of four subscales with 25 items, each of which is a seven-point Likert scale	• To identify factors that impede or facilitate adherence to anti-hypertensive medications	• Internal consistency: Cronbach's alpha = .63 - .80 • Test-retest reliability: Intraclass Correlation Coefficient = .79 - .86	• Construct validity: EFA indicated that the factor structure was best described by four factors • Convergent validity: There is a significant associations between the score on MUAH-25 and the BMQ	• General practice clinics and pharmacies	• No
Maastricht Utrecht Adherence in Hypertension (MUAH)-16	• Portugal	• Hypertension	• Consists of four subscales with 16 items, each of which is a seven-point Likert scale	• To identify factors that impede or facilitate adherence to anti-hypertensive medications	• Internal consistency: Cronbach's alpha =.64	• Convergent validity: The score of MUAH-16 is correlated positively and significantly with that of the MMAS-8 and Measure of Treatment Adherence (MAT) Scale • Construct validity: EFA indicated that the factor structure was best described by four factors. CFA showed very good fit to the data ($\chi^2$100 = 171.07, p<.001, CFI = 0.92, RMSEA = .04)	• Local pharmacies	• No
Treatment Adherence Questionnaire for Patients with Hypertension (TAQPH)	• China	• Hypertension	• Consists of six subscales with 33 items, each of which is a four-point Likert scale	• To identify adherence level of hypertensive patients • To identify factors resulted in non-adherence to anti-hypertensive medications	• Internal consistency: Cronbach's alpha =.86 • Test-retest reliability: Intraclass Correlation Coefficient =.82	• Criterion-related validity: The score of TAQPH is positively correlated with that of MMAS (r = .76, p< 0.01), and GSES (r = .69, p<.01) • Content validity: Assessed by a panel of nine experts • Construct validity: EFA indicated that the factor structure was best described by six factors. CFA showed good fit to the data (χ^2/ df = 1.91, RMSEA = .042, CFI = .96)	• Hospital	• No
Hill-Bone Compliance Scale (HBCS)	• United States	• Hypertension	• Consists of 14 items, each of which is a four-point Likert scale	• To identify barriers preventing medication adherence	• Internal consistency: Cronbach's alpha = .74 -.84	• Content validity: Assessed by a panel of eight experts • Construct validity: EFA indicated that the factor structure was best described by a single factor	• Outpatient clinic	• No
Self-Efficacy for Appropriate Medication Use Scale (SEAMS)	• United States	• Multiple chronic diseases including hypertension	• Consists of 13 items, each item is a three-point Likert scale	• To identify barriers preventing medication adherence	• Internal consistency: Cronbach's alpha = .89 • Test-retest reliability: Spearman correlation = .57	• Criterion-related validity: The score of SEAMS is strongly correlated with that of MMAS-4 • Construct validity: EFA indicated that the factor structure was best described by two factors	• Outpatient clinic in a hospital	• Yes, Bandura's Social Cognitive Theory

10 to 20 participants. These participants will not be recruited for Phase 2 to avoid confounding bias.

Participants Recruitment

Participants will be recruited for this study if they are (a) at least 18 years old, (b) diagnosed with hypertension with a persistent elevation of systolic blood pressure of 130 mmHg or greater and/or diastolic blood pressure of 80 mmHg or greater, or currently prescribed with anti-hypertensive drugs, (c) on anti-hypertensive drug treatment for at least six months, and (d) able to communicate in English language or Bahasa Malaysia. Psychiatric patients are eligible too if they are (a) aged at least 18 years old, (b) able to give consent independently, and (c) have no suicidal tendency at the time of study recruitment. Written consent forms, patient information sheets describing the study, and ethical approval letters will be provided to the participants who agree to participate.

On exclusion criteria, no participants will be recruited for this study if they are diagnosed with (a) secondary hypertension such as parenchymal kidney disease, renovascular disease, primary aldosteronism, Cushing syndrome, and phaeochromocytoma, (b) malignancies, (c) cognitive impairment and mental health disorders such as schizophrenia, major depressive disorder, generalised anxiety disorder, and dementia, and (d) pregnant. Patient history and medical records will be used to establish exclusion criteria.

Data Collection

A semi-structured interview schedule will be developed according to the four-step Interview Protocol Refinement (IPR) Framework in setting up the interview schedule to ensure validity and reliability (26). In Step 1, we will design a series of open-ended questions in the interview schedule based on our research objective as described above. In Step 2, we will construct all interview schedule questions in an inquiry-based conversation fashion (e.g., can you please share with me your experience with high blood pressure?). The questions will be in English so that participants from different sociodemographic subgroups can easily understand them. In Step 3, we will invite two members of the supervisory committee and an external primary care physician to review the interview schedule and provide feedback independently. Finally, in Step 4, we will test the newly developed interview schedule with two hypertensive patients, one from each health clinic. Subsequently, an independent translator will translate the validated interview schedule into Bahasa Malaysia.

All interview sessions will be conducted in a quiet meeting room at the clinics. We will begin the session by discussing the purposes of the interview. Participants will be asked to introduce themselves to build rapport. They will also be encouraged to share their thoughts and ideas freely. We will elicit the domains of adherence and non-adherence to anti-hypertensive drugs among the participants through all questions in the interview schedule. We aim to complete the interviews within 45 minutes, and each session will end with the interviewer's reflection. All sessions will be audiotaped and transcribed verbatim. Recruitment of participants will proceed until the point of thematic saturation. All data collected will remain private and confidential.

Data Analysis

After each interview, we will save the audio files on a password-secured laptop and transcribe verbatim the audio using NVIVO software. Transcripts will be then checked against the audio recording of each interview to ensure accuracy. Participant names will be replaced with coded names for confidentiality purposes. Should the interviews be conducted in Bahasa Malaysia, we will translate the recordings into English. A constant comparative method will be used for analysis. Specifically, we will read through the transcripts before extracting and coding the meaning units. Then, we will categorise the codes. We will ensure the quality and rigour of the qualitative inquiry through the tests of credibility, transferability, dependability, and confirmability.

We aim to achieve the credibility of the current study through triangulation and member checks. Two independent investigators will analyse the same data set and compare the findings using the triangulation process. Member checks will also be performed by taking the analysed data back to the hypertensive patients for verification. We will ensure dependability through peer review and researcher reflexivity. Peer review will be done by inviting a qualitative researcher to evaluate the raw data and examine whether the research findings are plausible according to the interview data. In addition, the interviewers will also clearly mention their dispositions, biases, worldview, assumptions, theoretical orientation, and relationship to the study that may affect the investigation. We aim to achieve transferability through the rich and thick description of the study setting and the characteristics of the participants (e.g., age, gender, ethnicity, & level of education of the hypertensive patients). Confirmability will be ensured through the provision of verbatim.

All audio recordings will be de-identified, and there will be no mention of personal identifying information (e.g., names, identification card number, and address) during the interview. All audio recordings are for transcription purposes and will not be copied or transferred to any other parties or used for any other purposes. After transcription, the audio recordings will be disposed of securely. We will store all audio recordings in the form of voice recording MP3 until the completion of transcription. The transcription will be saved in Microsoft Word format on a password-secured computer. Only the principal investigator and coordinator investigator

will have access to the data.

PHASE 2

We will conduct a quantitative study to develop and validate the Malaysian Anti-hypertensive Agents Non-Adherence Scale (MAANS) in a sample of hypertensive patients. This quantitative study is cross-sectional by design.

Item Generation

The preliminary version of the MAANS will consist of themes generated from Phase 1, which aimed to identify domains of adherence and non-adherence to hypertension treatment. Based on these themes, we will create the preliminary MAANS items. Thirty participants will be asked to individually and independently evaluate and score each MAANS item for appropriateness, representativeness, and explicitness using a 4-point Likert scale ranging from 1 (irrelevant and should be deleted) to 4 (relevant, clear, and precise). Statistically, only items with a mean score of 3.0 or above will be retained. The decision to keep any preliminary MAANS items scoring below 3.0 rests with the experts. An experts panel consisting of A.I.N.M.N., K.A.T., and S.Q.Y. will determine the appropriateness of whether to delete or retain an item. Hence, the preliminary version of the MAANS.

The Pilot Version

Pilot testing helps to ensure that items are meaningful to the Malaysian hypertensive population. The pilot study is needed to minimise misunderstandings and subsequent measurement errors and eliminate poorly worded items. We will conduct cognitive interviews with 5 to 15 hypertensive patients. During the interview, participants will have a chance to augment, clarify, and modify each preliminary MAANS item so that the item is more precise, culturally accepted, and not time-consuming. This process will result in the pilot version of the MAANS.

Participants Recruitment

In Phase 2, data collection and participant recruitment will also take place at the two participating health clinics located in Kuala Lumpur as in Phase 1. Eligible patients who attend these two clinics from June 2021 to December 2021 will be randomly selected.

As for sample size calculation, data of at least 200 participants is needed to run factor analysis (27). Hence, a final sample of 400 participants will be recruited. Of these, data from 200 participants (serving as the calibration sample) will be subjected to exploratory factor analysis (EFA), and data from 200 participants (serving as the validation sample) will be subjected to confirmatory factor analysis (CFA). All participants will be selected according to the inclusion and exclusion criteria described in Phase 1.

Measures

Participants will complete a research questionnaire using either a printed or online survey containing sociodemographic items (e.g., age, gender, ethnicity, level of education, marital status, employment status) and the pilot version of the MAANS. We aim to design a questionnaire with not more than 100 items to prevent respondent fatigue (28). Scores on all items are summed to obtain a total score, where higher total scores represent poorer adherence.

The Modified Version

We will examine the factor structure of the pilot version of the MAANS with the calibration sample. A Maximum Likelihood with Promax rotation will be conducted to determine the factor structure of the pilot version of the MAANS. In particular, the following criteria will be used to determine the number of items and number of factors in the instrument: (i) items shall have communality ≥ 0.2; (ii) items must contain factor loadings ≥ 0.30; (iii) items must not cross-load on two or more factors with loading values ≥ 0.32; (iv) items must have conceptual clarity; (v) items must load on a factor with at least three items. When this is done, we will obtain the modified version of the MAANS.

The Final Version

We will examine the factor structure of the modified version of MAANS with the validation sample. CFA will be performed to examine the goodness-of-fit of MAANS' measurement model. The measurement model is then evaluated by the relative chi-squared (χ^2/df) test, Root Mean Squared Error of Approximation (RMSEA), Standardised Root Mean Squared Residual (SRMR), and Comparative Fit Index (CFI). Acceptable model fit is indicated by χ^2/df < 3.0, RMSEA < 0.08 and SRMR < .8. The values of CFI should be 0.90 or greater (29).

Test for Validity

The predictive validity of MAANS will be evaluated against the Malay version of WHOQOL-BREF using the multiple regression analysis (30). The 26-item WHOQOL-BREF is a self-report scale developed by the World Health Organisation to measure the quality of life. Item 1 and item 2 ask about an individual's overall perception of their health. In contrast, the remaining 24 items assess an individual's quality of life in 4 domains, namely physical, psychosocial, social, and environment. Participants rate items on a 5-point Likert scale in which higher scores denote better quality of life. We hypothesise that the total score of MAANS is negatively correlated with that of WHOQOL-BREF (i.e., the poorer the adherence to anti-hypertensive medications, the lower the quality of life).

Test for Reliability

The internal consistency of the final version of the MAANS will be evaluated by Cronbach's alpha coefficient. An alpha coefficient of > .70 is acceptable

while > .80 is considered good internal consistency (23).

Ethics Approval

Ethical approval is granted by the Medical Research Ethics Committee, Ministry of Health, Malaysia (MREC) prior to the study (reference no: NMRR-18-3251-44694). All researchers involved in this study will comply with the principles of the Declaration of Helsinki and the Malaysian Good Clinical Practice Guidelines.

DISCUSSION

Maintaining a high level of adherence to anti-hypertensive medications is vital to ensure satisfactory blood pressure control (31). Unfortunately, even though this concept is made clear to the public via various health promotion programmes from time to time, many patients still present with hypertensive complications, primarily due to unidentified and unattended barriers to adherence (31).

To address such unmet needs, the objective of the present study is twofold. First, through quantitative inquiries, we aim to identify the domains of adherence and non-adherence to anti-hypertensive medications among hypertensive patients. Secondly, we intend to develop and validate an anti-hypertensive drug adherence scale, called the Malaysia Anti-hypertensive Agents Non-Adherence Scale (MAANS), through a quantitative approach. This newly developed questionnaire can be used to measure adherence to anti-hypertensive medications in a health clinic setting. In addition, it can precisely pinpoint the underlying barriers to adherence among patients who do not adhere to their medications.

One of the advantages of the study is that we will use WHOQOL-Bref Malay version to assess the predictive validity of MAANS. The Malays version of WHOQOL-Bref has been subjected to rigorous validation in the local population and demonstrates moderate-to-good reliability and validity (32). Secondly, we designed the semi-structured interview schedule based on the four-step Interview Protocol Refinement Framework (26). With this framework, open-ended questions were constructed in an inquiry-based conversation fashion to accommodate participants from different sociodemographic subgroups, considering Malaysia is a multi-ethnic country. Thirdly, we will distribute the questionnaires via printed and online formats to increase the response rate. Eligible participants will be contacted via phone to brief them about the survey and to obtain their consents. We hope to achieve a higher response rate, efficiency, and cost-effectiveness using these sampling strategies.

There are, however, a few limitations associated with this study. First, our results cannot be generalised to the entire Malaysian population since we will only recruit participants attending two health clinics in Malaysia's capital city. Secondly, including only outpatients as respondents from public health clinics and not from private healthcare institutions may have selection bias. However, it was reported that most hypertensive patients receive their treatment and follow-up at public health clinics (33); hence, the sampling from these settings should be appropriate.

CONCLUSION

In conclusion, we believe that this study will provide substantial and in-depth insight into the underlying domains of adherence and non-adherence to anti-hypertensive medications. From these domains, we will synthesise a local questionnaire (MAANS) that is reliable and valid to measure the adherence level in hypertensive patients. This questionnaire will help healthcare professionals to understand the relative importance of different factors of drug adherence and how they interact with each other. Such information will eventually assist the Ministry of Health in policy-making and guide public health officials to design effective health promotion programmes and evidence-based interventions to reduce complications of uncontrolled hypertension. Better-controlled blood pressure can reduce cardiovascular disease, relieving the government's health care burden. Improving adherence may also result in a more cost-effective hypertension treatment in Malaysia.

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