EVALUATION OF THE PERCEPTION AND EFFECTIVENESS OF CALENDAR BLISTER PACK INTERVENTION ON MEDICATION ADHERENCE AND CLINICAL OUTCOME AMONG HYPERTENSIVE PATIENTS AT KULIM HOSPITAL, MALAYSIA. A MIXED METHODOLOGY APPROACH

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by

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TABLE OF CONTENTS

ACKNOWLEDGEMENT ii

TABLE OF CONTENTS iv

LIST OF TABLES ix

LIST OF FIGURES xi

LIST OF ABBREVIATIONS xii

ABSTRAK xiv

ABSTRACT xvii

CHAPTER 1 GENERAL INTRODUCTION

1.1 Background 1

1.1.1 Hypertension 3

1.1.2 Guidelines for hypertension 3

1.1.3 Prevalence of hypertension 6

1.1.4 Burden of hypertension 8

1.1.5 Factors affecting blood pressure control 10

1.2 Overview of thesis 15

CHAPTER 2 LITERATURE REVIEW

2.1 Medication adherence 17

2.1.1 Definition of medication adherence 17

2.1.2 Intentional and unintentional non-adherence 20

2.1.3 Burden of medication adherence in hypertension 22

2.2 Measurement of medication adherence 24

2.2.1 Direct methods for assessing medication adherence 25

2.2.2 Indirect methods for assessing medication adherence 28

2.2.3 Ideal medication adherence measurement 47

2.3 Intervention to improve medication adherence 52

2.3.1 Educational intervention 52

2.3.2 Behavioural intervention 54

2.3.3 Social support intervention 55

2.3.4 Technical intervention 56

2.4 Calendar blister pack, CBP 57

2.4.1 Effectiveness of CBP on medication adherence 59

2.5 Literature review gaps 78

2.6 Problem statement 80

2.7 Study objectives 83

2.8 Rationale and significance of the study 83

CHAPTER 3 METHODOLOGY

3.1 Introduction 87

3.2 Research design 87

3.3 Ethical consideration 92

3.4 Focus group discussion 92

3.4.1 Study population and setting 92

3.4.2 Inclusion and exclusion criteria 93

3.4.3 Study procedure 93

3.4.4 Data collection 94

3.4.5 Data management and analysis 95

3.5 Randomized controlled trial 95

3.5.1 Study setting and duration 95

3.5.2 Population and sampling method 96

3.5.3 Selection criteria 96

3.5.4 Sample size calculation 98

3.5.5 Calendar blister pack, CBP intervention 99

3.5.6 Study procedure 100

3.5.7 Data collection/study instruments 105

3.5.8 Data analysis and interpretation 114

CHAPTER 4 RESULTS

4.1 Focus group discussion 122

4.1.1 Descriptive analysis of socio-demographic profile 122

4.1.2 Thematic analysis 125

4.2 Randomized controlled trial 133

4.2.1 Participants flow 133

4.2.2 Patient demographic characteristics 136

4.2.3 Validation 138

4.2.4 Medication adherence assessments 143

4.2.5 Blood pressure assessments 150

4.2.6 Bivariate relationship among study outcomes and study variables 151

4.2.7 Association between medication adherence and related factors 154

4.2.8 Association between blood pressure and study variables 157

4.2.9 Effect of medication adherence in predicting blood pressure 158

4.2.10 Odds ratio 159

4.2.11 Cost analysis 159

CHAPTER 5 DISCUSSION

5.1 Perception on the name, appearances and labelling of medicines 163

5.2 Benefits of CBP 166

5.3 Calendar blister pack versus pillbox organizer intervention 174

5.4 Factors associated with MMAS, MPR and percentage of on-time refill 175

5.5 Barriers of medication adherence..... 178

CHAPTER 6 CONCLUSION

6.1 Study limitations 186

6.2 Recommendation for future research 188

REFERENCES..... 191

APPENDICES

LIST OF PRESENTATIONS AND PUBLICATIONS

LIST OF TABLES

		Page
Table 2.1	Definition of the medication adherence measurement methods involving secondary database	39
Table 2.2	Summary of the advantages and disadvantages of adherence measurements	49
Table 2.3	Studies conducted to assess medication adherence, health outcomes and healthcare cost of CBP against normal, conventional packaging (1980-2017)	60
Table 3.1	Definition of healthcare resources cost	112
Table 3.2	Definition of sensitivity, specificity, positive and negative predictive value	118
Table 4.1	Patients' demographic characteristics in focus group discussions	124
Table 4.2	Summary of the themes emerged from the focus group discussion	125
Table 4.3	Patient's characteristics at baseline	137
Table 4.4	Relationship between medication adherence (MMAS, MPR and percentage of on-time refill) with other risk factors	140
Table 4.5	Relationship between MMAS and blood pressure control in patients	141
Table 4.6	Relationship between MPR and blood pressure control in patients	142
Table 4.7	Relationship between percentage of on-time refill and blood pressure control in patients	143
Table 4.8	Paired comparison of MMAS between intervention and control group	144
Table 4.9	MMAS score in high, medium and low adherence levels	145

Table 4.10	Patients' responses to the MMAS questionnaire	147
Table 4.11	Medication adherence measured by medication possession ratio	148
Table 4.12	Medication adherence measured by percentage of on-time refill	149
Table 4.13	Percentage of on-time refill by months	149
Table 4.14	Blood pressure assessments between groups	151
Table 4.15	Spearman's correlation analyses	153
Table 4.16	Unstandardized beta (*B*) coefficients and p-value for multiple linear regression predicting medication adherence	156
Table 4.17	Multiple linear regressions predicting blood pressure	158
Table 4.18	Effects of medication adherence in predicting blood pressure	159
Table 4.19	Mean of treatment cost for both groups	162

LIST OF FIGURES

		Page
Figure 3.1	Study flow chart	91
Figure 3.2	Appearance of calendar blister pack, CBP and normal blister pack	100
Figure 3.3	Randomized controlled trial workflow	104
Figure 4.1	CONSORT diagram displaying the flow of participants through the study	135
Figure 4.2	Total treatment costs for control and intervention group	161

LIST OF ABBREVIATIONS

CBP	Calendar Blister Pack
CI	Confidence Interval
CMA	Continuous, Multiple Interval Measure of Medication Acquisition
CMG	Continuous, Multiple Interval Measure of Gaps
CMOS	Continuous, Multiple Interval Measure of Oversupply
CONSORT	Consolidated Standard of Reporting Trial
CSA	Continuous, Single Interval Measure of Medication Acquisition
CSG	Continuous, Single Interval Measure of Medication Gaps
DALYs	Disability Adjusted Life Years
DASH	The Dietary Approaches to Stop Hypertension
HIV	Human Immunodeficiency Virus
JNC	Joint National Committee on Prevention, Detection, Evaluation and Treatment on High Blood Pressure
MAQ	Medication Adherence Questionnaire
MARS	Medication Adherence Rating Scale
MEMS	Medication Events Monitoring System
mg/dL	Milligrams per Decilitre
MMAS	Morisky Medication Adherence Scale
mmHg	Millimetre of Mercury
MPR	Medication Possession Ratio
OR	Odds Ratio

PDC	Proportion of Days Covered
prn	When Necessary
RM	Ringgit Malaysia
SD	Standard Deviation
Sdn Bhd	Private limited company
SEAMS	Self-Efficacy for Appropriate Medication Use Scale
SPSS	Statistical Package for Social Science Software
USD	United States Dollar

PENILAIAN PERSEPSI DAN KEBERKESANAN INTERVENSI KALENDAR BLISTER PEK TERHADAP PEMATUHAN UBAT DAN HASIL KLINIKAL DALAM KALANGAN PESAKIT HIPERTENSI DI HOSPITAL KULIM, MALAYSIA. METODOLOGI CAMPURAN

ABSTRAK

Tujuan kajian ini dijalankan adalah untuk meneroka persepsi terhadap pembungkusan ubat dan kalendar blister pek (CBP), menilai keberkesanan CBP terhadap pematuhan ubat, hasil klinikal (tekanan darah) serta kos rawatan yang berkaitan dengan intervensi tersebut dalam kalangan pesakit hipertensi di Hospital Kulim, Malaysia. Kajian ini melibatkan metodologi campuran, iaitu kaedah kualitatif dan kuantitatif. Dalam fasa I, dua sesi perbincangan kumpulan berfokus telah dijalankan dalam kalangan 16 pesakit hipertensi untuk mengumpul maklumat mengenai persepsi pesakit terhadap pembungkusan ubat dan CBP dalam rawatan penyakit hipertensi. Maklumat yang dikumpulkan diterjemahkan secara verbatim dan dianalisis dengan menggunakan kaedah analisis tematik untuk mengenal pasti tema-tema baru. Fasa II dalam kajian ini ialah percubaan klinikal terkawal rawak dengan hasil kajian fasa ini adalah pematuhan ubat, bacaan tekanaan darah dan kos rawatan untuk pesakit dalam kajian ini. Kos rawatan ini termasuk kos ubat-ubatan, lawatan klinik, kemasukan wad, prosedur perubatan dan ujian diagnostik. Kesahihan konvergen dan kumpulan yang diketahui telah dijalankan untuk mengesahkan alat pengukuran kepatuhan yang diguna dalam kajian ini. Analisis tematik menghasilkan tiga tema utama iaitu pengetahuan dan kebiasaan terhadap nama ubat dan pembungkusan ubat; persepsi mengenai pembungkusan dan label ubat-ubatan; pengetahuan dan pandangan terhadap CBP. Setiap tema utama tersebut mengandungi

dua atau tiga subtema. Pesakit hipertensi yang menyertai perbincangan kumpulan berfokus ini bersetuju bahawa CBP adalah suatu intervensi yang hebat untuk meningkatkan kesedaran pesakit tentang kekerapan penggunaan ubat, meningkatkan pematuhan ubat dan mengurangkan kesilapan penggunaan ubat-ubatan. Dalam percubaan klinikal terkawal rawak, seramai 83 pesakit hipertensi, yang sedang menerima rawatan untuk hipertensi dengan menggunakan ubat amlodipine, telah direkrut dan dibahagikan secara rawak ke dalam kumpulan intervensi (N=41) dan kumpulan kawalan (N=42). Pesakit-pesakit ini dijadualkan untuk melawat farmasi yang menjalani kajian ini setiap 28 hari, selama tujuh bulan dalam tempoh pengajian, untuk mengisi preskripsi mereka. Kajian ini mendapati bahawa pesakit dalam kumpulan intervensi mempunyai skor pematuhan ubat yang lebih baik pada akhir kajian ini berbanding dengan kumpulan kawalan, dengan menggunakan skala kepatuhan ubat Morisky (7.414 berbanding 6.796, $p<0.05$); nisbah pemilikan ubat (0.991 berbanding 0.979, $p<0.05$); peratusan pengisian preskripsi yang tepat pada masanya (0.992 berbanding 0.929, $p<0.05$). Selain itu, kumpulan intervensi menujukkan bacaan tekanan darah yang lebih rendah berbanding dengan kumpulan kawalan (123.590/78.057mmHg berbanding 129.728/81.360mmHg, $p<0.05$). Dari perspektif hospital, purata kos rawatan tahunan bagi pesakit dalam kumpulan intervensi adalah RM 2178.66 (95% CI 1786.39-2570.94) berbanding dengan RM 2693.09 (95% CI 1903.23-3482.95) dalam kumpulan kawalan. Di samping itu, kajian ini mendapati bahawa skala kepatuhan ubat Morisky tidak berkiat rapat dengan nisbah pemilikan ubat dan peratusan pengisian preskripsi yang tepat pada masanya ($p>0.05$). Unutk kesahihan kumpulan yang diketahui, usia pesakit dan tekanan darah berkiat rapat dengan skala kepatuhan ubat Morisky ($p<0.05$). Manakala, pesakit yang telah didiagnosis dengan hipertensi kurang dari lima tahun mempunyai nisbah pemilikan

ubat yang lebih tinggi berbanding dengan persakit yang telah didiagnosis hipertensi lebih daripada lima tahun ($p<0.05$). Kesimpulannya, kajian ini telah memberi gambaran tentang pendapat, persepsi dan pengalaman pesakit hipertensi terhadap pembungkusan ubat dan ubat-ubatan CBP. Selain itu, kajian ini juga membuktikan bahawa CBP mempunyai kesan positif terhadap pematahuan ubat, bacaan tekanan darah dan mempunyai potensi untuk penjimat kos rawatan yang agak memuaskan dalam kalangan pesakit hipertensi.

EVALUATION OF THE PERCEPTION AND EFFECTIVENESS OF CALENDAR BLISTER PACK INTERVENTION ON MEDICATION ADHERENCE AND CLINICAL OUTCOME AMONG HYPERTENSIVE PATIENTS AT KULIM HOSPITAL, MALAYSIA. A MIXED METHODOLOGY APPROACH

ABSTRACT

This study aimed to explore patients' perception on medication packaging and calendar blister pack (CBP), to assess the effectiveness of CBP intervention towards medication adherence, clinical outcome (blood pressure) as well as the cost associated with the said intervention among hypertension patients in Kulim Hospital, Malaysia. A mixed methodology approach which involved both qualitative and quantitative methodology were implemented in this study. In phase I study, two focus group discussions were conducted among 16 hypertensive patients to collect data on patient's perception towards medication packaging and CBP medications in managing hypertension. Collected data were transcribed verbatim and analysed by thematic analysis to identify the emerging themes. Phase II in this study was designed as a randomized controlled trial with the study outcomes were medication adherence, blood pressure level and treatment costs which included costs for prescribed medications, clinic visit, hospitalization, medical procedure and diagnostic test. Convergent and known group validity were performed to validate the adherence measurement tools used in this study. The thematic analysis yield three major themes which were knowledge and familiarity with the medicine names and their packaging; perception about the packaging and labelling of medicines; the knowledge and views of CBP. Each of this theme was further divided into two or three subthemes. Patients agreed

that CBP is a great intervention to increase patient awareness on regular medicines use, enhance medication adherence and reduce medication errors. In randomized control trial, a total of 83 hypertensive patients who are currently on amlodipine treatment were recruited and randomly assigned into intervention (N= 41) and control group (N= 42). These patients were scheduled to visit the study pharmacy to refill their prescription every 28 days for seven months study period. This study found that patients in the intervention group have better medication adherence score at the end of this study compared to the control group as measured by Morisky medication adherence scale (7.414 versus 6.796, $p<0.05$); medication possession ratio (0.991 versus 0.979, $p<0.05$) and percentage of on-time refill (0.992 versus 0.929, $p<0.001$). Besides, intervention group demonstrated significant lower blood pressure level than control group (123.590/78.057mmHg versus 129.728/81.360mmHg, $p<0.05$). From the provider perspective, the average annual treatment cost per patient in the intervention group was RM 2178.66 (95% CI = 1786.39-2570.94) compared to RM2693.09 (95% CI 1903.23-3482.95) in the control group. Besides, Morisky medication adherence scale was no significantly associated with medication possession ratio and percentage of on time refill in this study ($p>0.05$). For known group validity, patient age and blood pressure were significantly associated with Morisky medication adherence scale ($p<0.05$). While, for patients who have been diagnosed with hypertension for less than five years have higher medication possession ratio compare to patient who have been diagnosed for more than five years ($p<0.05$). In conclusion, this study has provided an insight into the opinion and perception of hypertensive patients towards medication packaging and CBP medications. Besides, the study findings provided evidence that CBP has a positive

impacts on medication adherence, blood pressure outcome and has the potential for considerable cost savings among hypertensive patients.

CHAPTER 1 GENERAL INTRODUCTION

1.1 Background

Calendar blister pack (CBP) medication is an innovative unit-of-use (generally one month) packaging in which each pill's blister is incorporate with a simple daily labelling such as times (morning, afternoon, evening), day of week or date of the month (Zedler et al., 2011b). Various designs of CBP have been developed, however the basic features for the CBP are the pill in packing can easier be pushed out through the blister without any effort or spilling. The calendar feature on the packaging enable the patients to know the number of pills left and how long before the patient need to refill their prescription (Huff, 2009).

The first CBP medication was issued in 1963 for oral contraceptive Ortho-Novum with the intention to assist woman in adhering with their medications and this packaging gained good feedback from the user in improving their medication adherence (Gossel, 1999). Prior to CBP, most of the interventions (as education, counselling, reminder calls and risk communication) to improve patient adherence require active involvement of healthcare resources as they are generally complex, labour intensive and costly. Whereas, CBP is a simple and passive intervention which could enhance patient adherence at lower cost compared to those complex and labour intensive intervention.

The purpose of labelling the blister with calendar feature is to encourage the patients to follow the prescribed dosing schedule. Besides, it can provide a visual record to the patient on when is their last took of the medicines (Osterberg & Blaschke, 2005, Haynes et al., 2008). In addition, medications are clearly arranged in correct sequence

and interval which allow the patients to self-monitor the medication consumption, resulting in improvement of medication adherence and overall health outcome (Padigus, 2014). With the use of CBP, each pill stays and well protected in the blister pack until it is ready for consumption. Thus, the stability, efficacy and safeness of the medication are well protected by the blister pack.

In general, CBP medications are commonly used for oral contraceptives, corticosteroids, antibiotics and female hormone replacement therapy (Osterberg & Blaschke, 2005, Schneider, Murphy & Pedersen, 2008). Until lately, more medications are packed in CBP such as antiretroviral, antituberculosis, and psychiatric medication in order to enhance patient adherence (Finch et al., 2003, Abraham et al., 2016, Ng & Caires, 2016). However, CBP is still not commonly used for long-term medication to treat chronic diseases or other classes of daily dosed medications such as hypertension.

Poor medication adherence is a major problem in chronic diseases and studies reported that patient with chronic diseases only consume approximately 50% their medications prescribed by the healthcare professional (Sabaté, 2003, Brown & Bussell, 2011, Mathes et al., 2012). In addition, the total healthcare cost associated with poor medication adherence are approximately USD 106 billion per year in United States. Hence, medication adherence is one of the most important factor for managing chronic diseases. However, patient with chronic diseases usually required to consume several medications, as a result patient had difficulties to adhere to their medications. This thesis is to investigate whether the CBP intervention could improve medication adherence, clinical outcomes as well as the healthcare cost among hypertensive patients in Kulim Hospital, Malaysia.

1.1.1 Hypertension

Hypertension is a medical condition where the force of the blood is consistently pushing against the artery wall at a high pressure and eventually may cause serious health problems. Hypertension is a chronic disease which can be controlled through healthy lifestyle and diet, but cannot be cured by medication or prevented by vaccines (World Health Organization, 2013a, MedicineNet, 2016). It require life-time treatment plan to control this disease from progression (Goldstein, 2017).

Hypertension is a silent killer where people with high blood pressure basically do not suffer from any specific physical symptoms or illness on them. Hence, hypertension is usually detected only by regular check-up on the blood pressure reading. Ignoring hypertension may increase the risk of getting life-threatening health complications (Pierin et al., 2016). Reports showed that the higher the blood pressure level, the major organs in the body such as heart, brain and kidneys will be in higher risk of getting harmful consequences such as coronary artery disease, stroke, congestive heart failure, cognitive impairment and chronic renal disease (Chobanian et al., 2003, Whelton, He & Muntner, 2004, World Health Organization, 2013a).

1.1.2 Guidelines for hypertension

According to the recommendation by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC), normal blood pressure for healthy adults aged 18 years and above is defined as <120 mmHg / 80 mmHg. Whereas, prehypertension is defined as systolic blood pressure between 120 to 139 mmHg or diastolic blood pressure as 80 to 89 mmHg. Normal adults are considered to be on stage 1 hypertension if the systolic blood pressure is between 140

to 159 mmHg or diastolic blood pressure between 90 to 99 mmHg. Besides, stage 2 hypertension are those who with blood pressure ≥ 160 mmHg / 100 mmHg (Chobanian et al., 2003). In general, blood pressure ≥140 mmHg / 90 mmHg is consider hypertension, this guideline is accepted worldwide including World Health Organization, National Institute for Clinical Excellence, American College of Cardiology, American Heart Association and European Society of Hypertension (World Health Organization, 2005, National Institute for Health and Clinical Excellence, 2011, Mancia et al., 2013, Go et al., 2014, Weber et al., 2014). Whereas, for diabetes, chronic renal disease and certain cardiovascular diseases patients, their target blood pressure is slight lower, which is 130mmHg / 80mmHg (Chobanian et al., 2003).

In 2014, the 8th JNC report suggested to start pharmacological treatment on general population older than 60 years old with blood pressure ≥ 150 mmHg / 90 mmHg and the treatment goal is below 150mmHg / 90mmHg. The treatment goal for adults older than 60 years old is different from adults aged below 60 years old. Adults older than 60 years old have a higher systolic blood pressure as their treatment goal (150 mmHg / 90 mmHg) compared to the treatment goal for adults below 60 years old, (< 140 mmHg / 90 mmHg). Besides, pharmacological treatment should be initiated for adults younger than 60 years old with diastolic blood pressure of ≥ 90 mmHg. The targeted goal is below 90 mmHg. Whereas, in the population above 18 years old with either diabetes or chronic kidney disease, drug treatment to lower the blood pressure should be initiated at ≥ 140 mmHg / 90 mmHg and treatment threshold at < 140mmHg / 90mmHg (James et al., 2014).

In summary, the normal blood pressure for adults younger than 60 years old is < 120 mmHg / 80 mmHg (Chobanian, 2017). General population aged below 60 years old with a blood pressure of ≥140 mmHg / 90 mmHg is consider being hypertension and they are advised to start the pharmacological treatment according to JNC 8 guidelines. Besides, for adult age 60 years old and above, they are advised to initiate pharmacological treatment if their blood pressure is ≥ 150 mmHg / 90 mmHg (Chobanian et al., 2003, James et al., 2014).

A new guideline for prevention, detection, evaluation and management of high blood pressure in adults was release by American College of Cardiology and American Heart Association on November 2017. Based on this guideline, adults were consider to be normal blood pressure with the blood pressure below 120/80 mmHg, and patient was considered to be elevated blood pressure if the systolic blood pressure was between 120-129 mmHg and diastolic blood pressure was less than 80 mmHg. Patient was diagnosed with stage I hypertension if the systolic blood pressure between 130-139 mmHg or diastolic blood pressure between 80-89 mmHg. Patient was on stage II hypertension if the systolic blood pressure was above 140 mmHg or diastolic blood pressure at least 90 mmHg. Hypertensive crisis occur if the patient systolic blood pressure over 180 mmHg and/or diastolic blood pressure over 120 mmHg, patient need prompt changes in their medication if there are no other indications of problems, or patient need to be hospitalized if there are signs of organ damage (Whelton et al., 2017) .

1.1.3 Prevalence of hypertension

Hypertension have been identified as one of the risk factors for global disease burden and is the fourth contributor to premature death in developed countries such as United States (Lim et al., 2012, Forouzanfar et al., 2015). The prevalence of hypertension is increasing in both developed and developing countries. This increment might be due to the global economic development, urbanization as well as lifestyle changes in society (Yach et al., 2004, World Health Organization, 2011a).

According to World Health Organization global status report on non-communicable diseases 2014, the global prevalence of hypertension, defined as ≥ 140 mmHg / 90 mmHg, in adults aged 18 years old and above was around 22% (World Health Organization, 2014a). Among the World Health Organization regions, Africa has the highest prevalence of hypertension with 30% of the adults in Africa have high blood pressure. Whereas, the lowest prevalence was America. Only 18% of adults aged 18 and above in the region of America suffer from hypertension and the prevalence of hypertension in South-East Asia was 24.75% (World Health Organization, 2015). The number of hypertension patient rose dramatically from 600 million in 1980 to 1 billion in 2008, and by 2025, it is expected to increase to 1.56 billion globally (Kearney et al., 2005, World Health Organization, 2013a, World Health Organization, 2014a). This increment pattern was similar to the study done by Forouzanfar and colleagues, where they reported the projected number of adults aged 25 years and above with systolic blood pressure of ≥ 140 mmHg increased from 442 million in 1990 to 874 million in 2015 (Forouzanfar et al., 2017).

The prevalence of hypertension is reported to be high across different countries in Asia, ranging from 19% in Democratic People's Republic of Korea to 42% in Myanmar. In addition, there is a dramatically increment in the rate of hypertension among the countries in this region, such as India and Indonesia. The hypertension rate in India is reported to be only 5% in 1960s, nearly 12% in 1990s, and recently report showed that the percentage of adults with hypertension in India have increased to more than 30% in 2008 (Gupta, al-Odat & Gupta, 1996, Gupta, 2004, World Health Organization, 2011b). Next, the prevalence of hypertension in Indonesia rose from 8% in 1995 to 32% in 2008 (Krishnan, Garg & Kahandaliyanage, 2013). Lastly, World Health Organization reported that one in every three Asian adults suffer from high blood pressure (World Health Organization, 2013b).

In Malaysia, there was an upward trend in the percentage of adults aged 30 years and above who is hypertension. Studies showed that the prevalence of hypertension for adults above 30 years old was significantly increased from 32.9% in 1996, to 43.5% in 2011(Lim, Morad & Hypertension Study Group, 2004, Gurpreet et al., 2012). Besides, according to Malaysia National Health and Morbidity survey 2015, the prevalence of hypertension for Malaysian adults aged 18 years and above was 30.3%, which is estimated 6.1 million of the Malaysia citizen currently are suffering from hypertension and more than half of these patients are with undiagnosed hypertension (Ministry of Health-Institute for Public Health, 2015). As compared to neighbouring countries such as Indonesia (23.0%), Singapore (26.5%) and Thailand (20.5%), Malaysia (30.3%) had the highest hypertension rate among adults age 18 years and above (Kearney et al., 2005, Ministry of Health-Institute for Public Health, 2015). In general, men (30.8%) have a higher prevalence rate of hypertension compared to

female (29.7%) and 7 out of 10 elderly citizen above 60 years old suffered from high blood pressure (Ministry of Health-Institute for Public Health, 2015). Next, the prevalence of hypertension was significantly higher in rural areas (33.5%) compared to urban areas (29.3%) in Malaysia. The number of hypertensive patients in Malaysia population will continue to increase annually due to the progressive aging among the population unless comprehensive preventive intervention that focuses on improving awareness, treatment and control of hypertension is implemented among the general population (Abdul-Razak et al., 2016).

1.1.4 Burden of hypertension

Hypertension is a risk factor for cardiovascular disease such as coronary heart disease and it is the most important risk factor for stroke. Patient with hypertension has 4 times higher risk of getting stroke and caused approximately 50% of ischaemic stroke (Stroke Association, 2012, Arboix, 2015). Besides, patient with high blood pressure has 3.9 and 2.8 times higher risk in cerebral haemorrhage and aneurysmal subarachnoid haemorrhage respectively compared to those with normal blood pressure (van Gijn & Rinkel, 2001, Arboix, 2015).

On the other hand, World Health Organization research in 2004 showed that hypertension is estimated to cause 7.5 million deaths, approximately 12.8% of the total global deaths. Besides, hypertension is accounted for 57 million disability adjusted life years (DALYs) or 3.7% of total DALYs in the 2014 (World Health Organization, 2009). Globally, there is a rising trend in the number of death due to hypertension. In 2015, the annual number of deaths solely due to systolic blood pressure ≥ 140 mmHg

is 7.8 million or 14.0% of total global death, and has accounted for 143 million DALYs or 5.5% of the total DALYs (Forouzanfar et al., 2017).

In terms of economic impact, the annual average of treatment cost for hypertension from 2011 to 2012 in United States was USD 48.6 billion and from 2012 to 2013 is estimated to be USD 51.2 billion (Mozaffarian et al., 2015, Benjamin et al., 2017). This amount included the both direct and indirect cost of hypertension. The direct medical cost such as healthcare services, medication, hospitalization and home healthcare; and the indirect cost of lost productivity related to morbidity and mortality caused by hypertension (American Heart Association, 2005). Besides, the American Heart Association projected the treatment cost for hypertension would increase to USD 200 billion in 2030 (Heidenreich et al., 2011, Benjamin et al., 2017).

In Malaysia, there was a total of 37,600 hospitalization cases which were related to hypertension in 2005. The total cost of hospitalization is RM 110 million (Ong & Rozina, 2009). Besides, a total number of deaths due to complication of hypertension was increasing and it was about 52,000 cases in 2014. It was about 36% of the total death in Malaysia (World Health Organization, 2014b). The death rate due to hypertension and its complication in Malaysia (36%) is high as compared to the global statistics (12.8%) on the deaths caused by hypertension. In addition, the total healthcare expenditure had also increased from RM 8.30 billion in 1997 to RM 44.75 billion in 2013 (Ministry of Health Malaysia, 2015). The total healthcare expenditure would continue to increase due to the chronic diseases such as hypertension and increasing healthcare costs (Ramli & Taher, 2008).

1.1.5 Factors affecting blood pressure control

The main reason to treat hypertensive patients is to normalize the blood pressure and to prevent the disease progression which may lead to the cardiovascular event. However, in reality to control the blood pressure at the normal level is a challenging process by both healthcare provider and patients. Among the 71 million people in United States with high blood pressure, 48.2% of these individual do not have their blood pressure in control, which defined as ≥ 140 mmHg / 90 mmHg. Besides, among these individual with uncontrolled blood pressure, estimated about 13 million people are unaware of their blood pressure condition as well as not taking any antihypertensive medications (Nwankwo et al., 2013). A similar prevalence was found in Malaysia, whereby local studies showed that 51.7% of the hypertensive patients had poor blood pressure control (Cheong et al., 2015, Teoh et al., 2017). Besides, only 34.6% of the hypertensive patients in Malaysia know their blood pressure condition, and among these patients, only 32.4% were treated with antihypertensive medicines and among patients who treated with antihypertensive medicines, only 30.3% achieved the targeted blood pressure (Abdul-Razak et al., 2016).

Various studies have been conducted to determine the factors that affect blood pressure level among the patients (see Xu et al., 2013, Mungati et al., 2014, Alsolami, Correa-Velez & Hou, 2015, Nawata et al., 2017). These studies come into a conclusion that there are multiple factors that may affected the blood pressure level. These factors can be categorized as non-modifiable and modifiable factors. Non-modifiable factors such as patient age, gender and ethnicity are factors beyond an individual control to change or adjust it to prevent the disease. On the other hand, modifiable factors are factors that

can be changed or adjustable to prevent an individual from developing the disease, such as lifestyle factors and patient adherence (Ibekwe, 2015).

1.1.5.1 Non-modifiable factors

Personal factors such as age, gender and ethnicity or race are non-modifiable factors that may affect the blood pressure level.

Previous studies showed that the prevalence of hypertension in elderly individual aged 60 years and above is as high as 60% to 80% (Egan, Zhao & Axon, 2010, Lionakis et al., 2012, Seow et al., 2015). This might due to the progressive increase of the systolic blood pressure over the time for individual age from 30 to 80 years and above. While diastolic blood pressure increases only until the age of 50, then it will either decrease or becomes stable (Williams, Lindholm & Sever, 2009). Thus, there is 90% risk of developing systolic hypertension in a normal blood pressure individual after the age of 55 years (Chobanian et al., 2003). Besides, there is a linear relationship between high systolic blood pressure with cardiovascular event such as stroke among the elderly hypertensive patient (Borghi et al., 2003, Weitzman & Goldbourt, 2006, Brown, Giles & Greenlund, 2007).

Global data demonstrated that there is a higher percentage of men having high blood pressure compared to women until the age of 45. Age between 45 to 64 years old, the prevalence of hypertension is almost similar in both men and women; however, after the age of 64, women have a higher percentage of hypertension compared to men (Go et al., 2013). This might due to the female sex hormones such as oestrogen and progesterone which serve as the guardian for the blood pressure and heart. During the

menopause which usually happens in women around 45-60 years old, women start to loss their female sex hormones in their body; this might cause a rapid increase of blood pressure over the time. As a result, women have higher blood pressure after their menopausal (Dubey et al., 2002).

In Malaysia, the prevalence of hypertension is higher in other Bumiputras community (33.4%), follow by Indians (32.4%), Malays (31.1%) and lastly the Chinese community (30.8%) (Ministry of Health-Institute for Public Health, 2015). This might due to the different accessibility to the healthcare facilities, comprehensive prevention and control program that caused by geographical variation among different ethnicity (Wood & Euroaspire I and II Group, 2001). Other Bumiputras and Indians community mostly stay at the rural area; hence they may have limited accessibility to the healthcare services and regular healthcare screening, which might results in high prevalence among them (Abdul-Razak et al., 2016). Besides, various studies have been conducted globally on the racial and ethnic disparities in hypertension (see Hertz et al., 2005, Hicken et al., 2014, Dong et al., 2016, Krishnadath et al., 2016, Nguyen-Huynh et al., 2016, Cai et al., 2017). Studies found that the highest prevalence of hypertension in adults is African descent, follow by Asian or Hispanic, and lastly is Caucasians descent (cite Krishnadath et al., 2016).

1.1.5.2 Modifiable factors

Lifestyle behaviours such as dietary, salt intake, physical activity and stress level may have contributed to the high prevalence of hypertension in Malaysia. The Dietary Approaches to Stop Hypertension (DASH) trial and various studies conducted internationally have provided substantial data that a diet that is high in fibres (fruits,

vegetables and nuts) and potassium, low saturated fat dairy products, focus on chicken and fish rather than red meat, limiting alcohol consumption would lower the blood pressure and it is particularly effective among individual who are low sodium intake (Appel et al., 1997, Stranges et al., 2004, Streppel et al., 2005, Bazzano et al., 2013). Studies reported that a reduction of 3-6 gram of salt per day would reduce the systolic blood pressure by estimated 3.6 to 5.6 mmHg and 1.9 to 3.2 mmHg diastolic blood pressures (Graudal, Gallœ & Garred, 1998, He & MacGregor, 2003, Ha, 2014).

Besides, physical activity is one of the most commonly recommendation to hypertensive patients as it is widely accessible, inexpensive and effective in reducing the blood pressure (Huai et al., 2013). Regularly engage with physical activity such as aerobic exercise and brisk walking for at least 30-40 minutes per day, 3-4 times a week would decrease the systolic and diastolic blood pressure by 1.56 to 5 mmHg / 0.74 to 4 mmHg (Lakshminarayanan et al., 2012, Eckel et al., 2013). In addition, Yoga which included postures, breathing control and meditation had showed a significant effect on reducing the systolic and diastolic blood pressure, with an average decrease of 4.17 mmHg and 3.62 mmHg respectively (Hagins et al., 2013, Manchanda & Madan, 2013). Physical activities and yoga would benefit the hypertensive as well as normotensive individual if they adhere to these activities for long term.

Next, researches also demonstrated that hypertension patients who adhere to the healthy diet and lifestyle may reduce the systolic blood pressure from 2 to 14 mmHg (Appel et al., 2003, Dickinson et al., 2006, Eckel et al., 2013); However the effects of improvement in blood pressure is both patient and time dependent, hence, patients who are on strict diet and healthy lifestyle might have greater improvement compare to

those who are not. In additions, healthy diet and lifestyle not only assist in improving the blood pressure level but it also enhance the efficacy of the antihypertensive drugs and reduce the cardiovascular risk (Chobanian et al., 2003). Thus, in order to prevent hypertension and its related complications, healthy diet and lifestyle should be promoted among the patient with high blood pressure.

On the other hand, medication adherence is well-known as an important factor that affect not only the blood pressure among hypertension patient but also to other chronic diseases such as diabetes and hyperlipidaemia (Fischer et al., 2010). Medication adherence is defined as the extent to which patients consume their medication as prescribed by the healthcare professional with respect to dosing and frequency (Ho, Bryson & Rumsfeld, 2009). Previous studies showed that there is a significant association between blood pressure control and medication adherence (Wu et al., 2010, Iloh et al., 2013, Jesus et al., 2016, Piercefield et al., 2016, Khayyat et al., 2017). Due to the asymptomatic nature of hypertension, individual with high blood pressure usually are unaware about their blood pressure level and do not seek for treatment on their health condition (Ming et al., 2011, Yi-Bing et al., 2013). Even if they are aware and get treated, they usually are not adhere to their antihypertensive medication and have uncontrolled blood pressure (Pereira et al., 2009). This was proven by the global statistics, where the rate of blood pressure control among hypertension patient remain unsatisfactory, only 10-20% of the patient have achieved the targeted blood pressure control (Pereira et al., 2009, Whelton, 2015). In Malaysia, a study conducted in Kuala Lumpur showed that among the hypertensive patients who are on treatment, only half of these patients had controlled blood pressure (Chia & Srinivas, 2009). Thus, there is a need to improve medication adherence among hypertension patient. And, among the

intervention to improve medication adherence, the effectiveness of CBP intervention was not reported in Southeast Asia setting especially in Malaysia, whereby the prevalence of hypertension is high and adherence rate is low (Ministry of Health-Institute for Public Health, 2015).

1.2 Overview of thesis

In this thesis, Chapter Two reviews the literature related to the study with the definition of terminologies, types of medication non-adherence, followed by a brief discussion of the clinical and economic impotencies of medication adherence. This chapter continue with an overview of medication adherence and various measurement tools used to evaluate patients adherence. The pro and cons of each adherence measurements was discussed in depth in this chapter. This chapter is completed with a review of literature relevant to the study; focus on the effectiveness of CBP towards medication adherence, clinical and economic outcomes regardless of the disease, medications, study setting and population.

Methodologies use in this study were discussed in Chapter Three. A detail discussion of the methodology used for both qualitative and quantitative studies which included the reasons of selecting a particular method, study setting and statistical analyses is presented in this chapter. In addition, results interpretation of the selected adherence measurements and threshold for dichotomous adherence and blood pressure outcomes are discussed in this chapter.

Chapter Four will illustrate the findings of this study. The findings from focus group discussion conducted with hypertensive patients about their perception, opinion and

knowledge on medication packaging and CBP are discussed in this chapter. The validation results on selected adherence measurements and blood pressure are also presented in this chapter. Besides, this chapter reported the findings from randomized controlled trial which included the patient demographic characteristic, pre and post intervention assessment on adherence and blood pressure, as well as the treatment cost associated with study patients.

Chapter Five is a discussion chapter for this thesis. Patients' perception on name, appearance and labelling are discussed in this chapter. This chapter also included the reasons on how medication packaging and CBP medication affect patient adherence, the benefits of CBP and the factors associated with the selected adherence measurements. Last but not least, the potential barriers of medication adherence and the advantages of CBP against pillbox organizer can also be found in this chapter.

Chapter Six is the final chapter for this thesis. It summarized the overall findings for this study and draws a conclusion for this thesis. Besides, the limitations in this study and recommendation for further works can be found in this conclusion chapter.

CHAPTER 2 LITERATURE REVIEW

2.1 Medication adherence

This chapter provide an overview on the topics related to this study and a general review of the literature.

2.1.1 Definition of medication adherence

According to the former American surgeon Everett Koop, *"Drugs don't work in patients who don't take them"* (Osterberg & Blaschke, 2005). This phrase was then modified by Blaschke et al in 2012 to *"drugs work erratically in patients who take them erratically"*(Blaschke et al., 2012). In short, a medication effectiveness in treating a disease is depends on patient's behaviour in following the therapeutic regimen.

Various terms (e.g. compliance, adherence, persistence, and concordance) are being used to describe patient's behaviour in taking their medications prescribed by the healthcare professional. The most commonly-used terms are compliance and adherence. Even though these terms have been used interchangeably in explaining the patient's behaviour in continuing to take their prescribed medication, but their connotations are slightly different between these two terms. Compliance is a traditional term, which is defined as the extent to which patients obey the recommendation or instructions of healthcare provider (Lutfey & Wishner, 1999, Horne et al., 2005). Healthcare provider would layout the therapeutic goal and recommendation to achieve the goal, patients would then endure to the provider's authority and obey the order passively (Charavel et al., 2001, Treharne et al., 2006).

On the other hand, adherence is the extent to which patient followed the treatment regimen voluntarily as the healthcare provider have collaborate with the patients to improve patient's health by combining the provider's professional medical opinions with patient's lifestyle and preferences of care (Brown & Bussell, 2011). The term adherence also means that patients are more proactive and willing to have open discussion with the healthcare provider on their health related decision; and this term also focus on building a good collaboration between healthcare provider and patients in order to achieve the therapeutic goal (Swaminath, 2007). Thus, both healthcare provider and patients have the equal responsibilities on the outcomes of a treatment plan. Besides, adherence has been defined by World Health Organization as *"the extent to which a person's behaviour- taking medication, following a diet, and/or executing lifestyle changes corresponds with agreed recommendation from a healthcare provider"* (Sabaté, 2003).

In the current medical terminology, majority of the authors support and prefer to use the term adherence compared to compliance (Horne et al., 2005, Aronson, 2007, Chakrabarti, 2014). This might due to the reason that adherence is able to reflect the collaboration between patient and the healthcare provider in decision making related to their treatment plan (Osterberg & Blaschke, 2005). Whereas, the term compliance reflect the passive way where the healthcare provider decided a correct treatment plan for the patient, and patient has to comply or obey with the treatment plan regardless of its suitability or patient agreement on the treatment plan (Chakrabarti, 2014).

As compared to compliance and adherence, persistence and concordance are less commonly used by the healthcare provider or researchers. Concordance refers to an agreement between the provider and patient on the purpose of a treatment plan and the treatment regimen that the patient will consume (Aronson, 2007). Concordance does not refer to a patient's medicine-taking behaviour but emphasis on the nature of interaction between healthcare provider and patients on setting out the goals for therapy and not arbitrarily enforcing a treatment regimen (Bell et al., 2007, Fraser, 2010). This term may sometimes be used incorrectly as an interchangeably words for "adherence" and "compliance" (Hugtenburg et al., 2013). Persistence refers to *"the duration of time from the initiation to discontinuation of the therapy"*(Cramer et al., 2008). Although conceptually persistence and adherence are similar, but persistence is defined as how long patient will continuously stay with their treatment, and adherence refer to how well patient follow the treatment regimen as prescribed by the provider (Hugtenburg et al., 2013).

Medication adherence is usually being described as low or poor versus high or good adherence towards treatment regimen among patient. While, non-adherence refers to patient's resistance or refusal against properly adhere to the treatment regimen or therapy prescribed by the provider. In general, patient who suffer from acute disease would have high adherence rate compared to patients with chronic diseases (Sabaté, 2003). Patient adherence toward long term medication such as hypertension and diabetes is generally low, and usually drop dramatically after the first six months of the treatment (Osterberg & Blaschke, 2005). Non-adherence to medication prescribed by provider is a complex and multidimensional healthcare problem worldwide.

2.1.2 Intentional and unintentional non-adherence

There are many reasons why patient is non-adherence to their prescribed medication. Generally these reasons fall into two overlapping categories that is intentional and unintentional adherence (Lowry et al., 2005, Gadkari & McHorney, 2012, Molloy et al., 2014, Mukhtar, Weinman & Jackson, 2014).

Intentional non-adherence refer to non-adherence that is purposively and mainly associated with patient motivation. Patient with intentional non-adherence may have gone through a careful consideration to evaluate the pros and cons of a treatment before decided not to follow the treatment regimen and recommendation (Lowry et al., 2005, Clifford, Barber & Horne, 2008). Patient beliefs about medicine and disease, culture, and religion played an important role during this consideration or decision making process either to adhere or non-adherent to the regimen (Iihara et al., 2004, Goodfellow et al., 2013, Egenasi, Steinberg & Raubenheimer, 2015, Kumar et al., 2016).

Besides, patient might struggle during this consideration process as they might get information from medicine leaflet regarding to the side effect or other adverse effect of their medicine, and they might get confuse, lack of confident, or become sceptical about their treatment (Hugtenburg et al., 2013). In addition, certain treatment plan such as antiretroviral and mental therapy might stigmatize or remind the patient about their illness (Sirey et al., 2001, Sabaté, 2003). These factors might also influence patient's motivation to begin intentionally non-adherence with their medication or treatment plan.

Unintentional non-adherence refers to non-adherence that is mainly driven by limitation in capacity and resources to continue taking medications, as well as individual constraints such as memory and dexterity (Horne et al., 2005, Clifford et al., 2008). This is usually an unplanned behaviour and less likely to be associated with belief, culture, religious and side effect of the medication. Patient behaviour such as forgetfulness, missing dosages, losing medical attention, skipping appointments, inability to pay for treatment, difficulties in understanding the instructions and overloaded with medical information at once might lead to unintentional non-adherence in patients (Lehane & McCarthy, 2007, Bastakoti et al., 2013, Feldman et al., 2017).

Next, complexity of the medication regimen and complicated schedule for patients to take their medication might also result in unintentional non-adherence. For instance, drug-drug interactions such as tetracyclines or bisphosphonates should be taken separately from painkiller, calcium, aluminium, magnesium or iron salts. Some painkiller such as aspirin and ibuprofen can cause irritation at oesophagus if the patient ingest it with bisphosphonates. Where as, calcium would interfere with the absorption or lower the bioavailability of the bisphosphonates if it were taken together with bisphosphonates (Cascorbi, 2012). Thus, bisphosphonates should be consumed 30 minutes before meal and taken separately from other medicines. Besides, patient are required to maintain on upright posture for 30-60 minutes after taken bisphosphonate with a full glass of water (Rizzoli et al., 2011). Due to this complex and complication medication taking schedule, patient might hardly adhere to their medicines, as they might have poor recall of the instructions (Hugtenburg et al., 2013).

2.1.3 Burden of medication adherence in hypertension

Medication non-adherence is common among patients. The prevalence of adherence to chronic medication regimens is dramatically low as compared to acute diseases (Sabaté, 2003). This situation was clearly reflected in hypertensive patients, whereby approximately 43% to 80% of the hypertensive patients fail to adhere to their prescribed medications (Sabaté, 2003, Van Wijk et al., 2005, Burke et al., 2006, Kulkarni et al., 2006, Elliott, 2008, Klootwyk & Sanoski, 2011, Krousel-Wood et al., 2011, Barreto et al., 2015, Abegaz et al., 2017). The higher percentage of non-adherence rate was found among African populations such as Ivory Coast (87.5%), Togo (83.7%), Congo (78.8%) and Tunisia (63.4%); followed by Asians (43.5%), Europeans (36.6%) and Americans (36.6%) (Konin et al., 2007, Ghozzi et al., 2010, Abegaz et al., 2017). The discrepancies of non-adherence rate may be due to differences in the population studied, ethnic or cultural differences, sample size, as well as difference in the adherence measurement methods in the studies.

Besides, approximately 16% to 50% of the patients who are newly diagnosed with hypertension have stopped their medication within the first 12 months after their first antihypertensive regimens (Jones et al., 1995, Flack, Novikov & Ferrario, 1996, Vrijens et al., 2008, Azizi et al., 2016). In addition, a study conducted among 4783 hypertensive patients found that on each day, 10% of these patients who are still engaged with the antihypertensive regimens omitted their scheduled doses of medication (Vrijens et al., 2008). According to Bailey et al, this small deviations in medication adherence can be clinically important, as increasing patient adherence to antihypertensive medication by just one pill per week for daily regimen could reduce the risk of stroke by 8-9% and death by 7% (Bailey et al., 2010).

Non-adherence to antihypertensive medication is one of the important factor that lead to uncontrolled blood pressure among the patients (Sabaté, 2003, Bramley et al., 2006). Among patients who are non-adherence to their antihypertensive medication, approximately 62.4% to 83.7% of them were uncontrolled blood pressure patients (de Oliveira-Filho et al., 2014a, Abegaz et al., 2017). A recent meta-analysis suggested that an increase of 10 mmHg in systolic blood pressure in hypertensive patients with systolic blood pressure above 130 mmHg, would increases the risk of major cardiovascular disease events by 20%, coronary heart diseases by 17%, 27% of stroke, 28% of heart failure, and all-cause mortality by 13% (Ettehad et al., 2016). Thus, failure to achieve the targeted blood pressure level would increases the hazard of myocardial infarction, stroke, cardiovascular mortality and hospitalization (Lewington et al., 2002, Ho et al., 2008, Kettani et al., 2009, Wong et al., 2013).

Next, poor medication adherence was also associated with greater risk of mortality and higher hospitalization rates among patients (Pesa et al., 2012, Bitton et al., 2013, Shin et al., 2013, Kim et al., 2016b). Hypertensive patients who are non-adherent to their medication have 5.4 times higher risk of premature death compared to patients who adhere to their regimens (Gwadry-Sridhar et al., 2009). In addition, a cohort study conducted among 59,647 hypertensive patients in Canada reported that patients who are low adherence to their treatment regimens was 17% higher risk of hospitalization (Dragomir et al., 2010). Indirectly, non-adherence to treatment regimens would increase the healthcare costs due to disease progression, hospitalization and rehospitalisation among patients.

In United States, it is estimated that a total of USD 105 billion is wasted annually due to medication non-adherence. Among the chronic diseases, hypertension is one of the top three chronic diseases with the highest avoidable cost, which amount up to 18.6 billion annually. Approximately 69% of the avoidable costs is spent on the avoidable hospitalization cost (IMS Institute for Healthcare Informatics, 2013). While, other direct medical costs such as ad hoc service utilization at emergency department, comorbidity conditions, and addition diagnostic test resulted from the progression of the disease; these costs can be avoided if the patient adhere to their treatment regimens and control the disease at the primary stage (Iugo & McGuire, 2014). Besides, studies showed that if hypertensive patient adhere to their treatment regimens, it would save up to an averagely USD 3,908 per patients annually and reduced the total hospitalization cost by more than 25 million per year (Dragomir et al., 2010, Roebuck et al., 2011).

In summary, the global prevalence of medication non-adherence is high among chronic diseases patients. Non-adherence to antihypertensive treatment regimen is associated with the progression of the disease, poor health-related quality of life, increased healthcare utilisation and costs. Future development of measures to improve medication adherence is urgently needed to fully address these issue.

2.2 Measurement of medication adherence

Assessing medication adherence is a big challenge yet important component for both researchers and clinicians in the process of developing intervention to improve adherence among the patients. Accurate evaluation of patient adherence would provide a clear picture of the risk factors, consequences and strategies to improve patient