Guiding Hypertension Management Using Different Blood Pressure Monitoring Strategies (GYMNs study):

A Randomized Controlled Trial Comparing Unattended Automated Office Blood Pressure vs. Home Blood Pressure vs. Central Blood Pressure Monitoring for the Management of Hypertension

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Abstract

Introduction:

Home blood pressure (BP) and unattended automated BP (uAOBP) monitoring have been suggested by guidelines in the care of hypertensive subjects. Moreover, BP measurements in the peripheral arteries cannot serve as direct substitutes for their central counterparts. However, comparative effectiveness and safety between BP-guided strategies using these BP measuring devices have never been evaluated.

Methods and analysis:

Patients with uncontrolled or newly diagnosed hypertension aged 20-90 years will be recruited via outpatient clinics and allocated into three arms by stratified randomization (baseline systolic BP 130-155 mmHg and 155-180 mmHg): home BP, uAOBP, and central BP-guided treatment. Patients and physicians will be blinded to the allocated interventions by providing measured BP values in the clinic through a standardized report format. A common BP target with SBP 130 mmHg is adopted for these BP-guided strategies. The primary outcome is the change of 24 hour mean ambulatory SBP at 3 months. Key secondary outcome is to determine the proportions of achieving target BPs at 3 months and the decrease of left ventricular mass at 12 months.

Ethics and dissemination:

The study will be initiated in June 2018 and results are expected in 2020. The will provide randomized controlled trial evidence to support future guideline recommendations for optimal BP monitoring devices.

Introduction

Throughout middle and old age, blood pressure (BP) is strongly and directly related to vascular and all-cause mortality,[1] and lowering high BP has been shown to associate with a substantial risk reduction of cardiovascular diseases.[2] However, the traditional BP used for clinical practice, the office BP, is usually measured in a busy and hurry clinical environment, and interfered by the well-known confounding whitecoat effect.[3 4] As such, unattended automated office BP monitoring (AOBP) has been proposed as an effective solution[4] and further promoted by Canadian physicians.[5] Nonetheless, out-of-office BP, home BP and ambulatory BP, remains the methodology of recommendation for the detection of whitecoat effect, [6-8] and its prognostic value has been demonstrated to be superior to the traditional office BP.[9] In previous systematic review and meta-analysis, home BP has been shown to be as good as ambulatory BP in predicting target organ damage[10] and a better guiding strategy than conventional office BP.[11] Home BP monitoring, with its ability to detect morning and masked hypertension and a better tolerability than ambulatory BP monitoring for long-term use, can therefore be considered as a strategy of choice to replace office BP monitoring for guiding hypertension management.

Moreover, BP measurements in the peripheral arteries cannot serve as direct substitutes for their central counterparts because of the long-recognized differences

of blood pressure (BP) waveforms [12] and values [13] between the central aorta and peripheral arterial system. Thus, if the decisions on medication adjustment are made solely based brachial BP, there could be a considerable risk of over- or undertreatment.[14]

Considering that there are many better strategies for guiding hypertension management than traditional office BP, there is an apparent need for investigating their comparative effectiveness and safety in the management of hypertension. We hypothesized that home BP may be non-inferior to AOBP and central BP-guided intervention in reducing ambulatory BP and designed the present randomized controlled trial.

Method

Study Design and rationale of the reference standard: invasively measured CBP

This is a 12-month, prospective, randomized trial. The study is scheduled to commence in June 2018. We estimate to enroll a total of 252 patients with 84 subjects allocated into 3 arms. Details of the sample size calculation is provided in the statistics section.

Study Population

Patients with hypertension will be recruited via outpatient clinics and advertisement and in our hospital. Inclusion criteria are as follows: 20 to 90 years of age; nonpregnant; receiving antihypertensive therapy for uncomplicated essential hypertension and taking ≥1 but ≤ 2 types antihypertensive drugs (to rule out complicated or resistant hypertension) or hypertension newly diagnosed by uAOBP (uAOBP >130 mmHg at screening visit). Exclusion criteria are as follows: Poor adherence to medication; unable to conduct self-measurement blood pressure; history of polycystic kidney disease; congestive heart failure (a recent assessment of left ventricular ejection fraction < 40% prior to screening visit); chronic kidney disease with estimated glomerular filtration rate < 30 mL/min/1.73m2 (MDRD) at screening visit; a recent document of severely abnormal LV mass index (>59 g/m2.7

in women and >64 g/m2.7 in men) prior to screening visit; secondary causes of hypertension; uncontrolled hypertension (uAOBP >180/100 mm Hg at screening visit); history of severe aortic valve disease; history of upper limb obstructive atherosclerosis; BP Differences more than 5 mmHg between both arms at screening visit.

Study protocol

Patients will be randomized to have hypertension management decisions made on the basis of the uAOBP, home BP, and central BP monitoring. Randomization will be done by using computer-generated randomization codes in 2 stratums with baseline systolic BP (uAOBP) 130-155 mmHg and 155-180 mmHg. The BP measurements on left or right arm will also be determined by randomization codes. To guide the management of hypertensive patients, medication adjustment will be made based on a published guideline[8] with the measured BP through different BP monitoring methodologies. The use of different devices to obtain BP for guiding the care of hypertensive patients is aimed to determine whether these BP monitoring may be of comparable clinical value in routine practice. To achieve this, intervention patients will have medications titrated to normalize these different BP values. The target BP level, SBP 130 mmHg, of these different BP monitoring strategies are based on the latest guideline.[8 15 16]

An overview of study protocol and acquired measures is presented in Table 1. Although we encourage the adjustment of medication being adhered to the practice guideline,[8 16] the choice of drug adjustment will be left to the discretion of the patient's attending doctor. During the measurement periods of home BP monitoring, no medication adjustment is allowable to preserve the comparability between different BP values. On the scheduled visits, the corresponding BP will be measured before meeting doctors and provided for clinicians to adjust patients' medication according to practice guideline.[8 16] In summary, if the measured SBP is well within the target BP without possible side effects caused by antihypertensive agents, no medication adjustment is required. If is the differences between measured SBP and target BP is less than 20 mmHg, the suggested maximal dose adjustment is 1 drug. If the BP differences are above 20 and 40 mmHg, addition of 2 drugs (or single pill combination) or 3 drugs (or single pill combination) are suggested, respectively. If low BP (less than 90/70mmHg) or any possible drug related side effects was noted, cautious adjustment of antihypertensive will be done. The dose adjustment and any possible side effects will be recorded throughout the whole study conduct period.

A sub-study will be performed to test the level of agreement between different measured BP values.

BP monitoring: uAOBP, central BP, and home BP

Firstly, BP will be taken simultaneously from both upper arms by an oscillometric BP monitor (WatchBP Office Central; Microlife AG, Widnau, Switzerland). Subjects with SBP Differences between both arms more than 5 mmHg will be excluded. The performance of BP measurements will be adhered to the standard BP measurements procedures. For the uAOBP and CBP, the measurements will be conducted in a quiet room without the presence of clinical personnel. Patients will be seated in a quiet room without talking and taken as an average of 3 measurements with an automated device (HEM-907, Omron Healthcare, Lake Forest, IL) that has been preset to wait 5 minutes before measurements.[3] Simultaneously, the central BP will be measured in the other upper arm. (WatchBP Office Central; Microlife AG, Widnau, Switzerland).[17] The determination of the right or left upper arm for uAOBP or central BP will be made in a random order by computer generated random codes before the enrollment. As for the home BP measurements, a validated device (WatchBP Home; Microlife AG, Widnau, Switzerland) will be provided for all subjects allocated to the home BP arm to measure their BP at home. Subjects are requested to take BP in the morning (within 2 hours after awakening) and afternoon before meals for 7 consecutive days before the scheduled clinical visits. BP in the first day of the measurements will be discarded and an average of home BP (all BP reading and BP in the morning and in the afternoon) will be generated and provided

for clinicians to guide their treatment. The ambulatory BP of all subjects will be measured at baseline, at 3 months, and at the end of the study by a validated device (WatchBP O3 AFIB Ambulatory). Similarly, the choice of right or left arm for the measurement of ambulatory BP will be determined in a random manner. All the automated BP readings are stored digitally for analysis and corresponding BP values in each arm will be provided for clinicians to guide their hypertension management.

Randomization, Outcomes, and Masking

Each patient will be randomly assigned, using a standard computer protocol at the General Clinical Research Center, Taipei Veterans General Hospital, Taipei, Taiwan, to intervention in a 1:1:1 ratio using sealed opaque envelopes (sequentially numbered). The study coordinator will oversee the enrollment and intervention assignment and keep allocation concealment. The Primary outcome is the change of 24 hour mean ambulatory SBP at 3 months. The secondary outcomes include the change of 24 hour mean ambulatory DBP at 3 months, decrease of left ventricular mass at 12 months, change of SBP/DBP measured by uAOBP monitoring, home BP monitoring, or central BP monitoring, change of quality of Life, change of medication count and side effects. Any possible treatment related side effects including hypotension, injurious fall, dizziness, electrolyte imbalance (serum Na <130meq/L, serum K > 5.5 or <3.0 meq/L), syncope, acute renal failure (increase in serum

creatinine > 1.5 times baseline, or increase in serum creatinine by ≥0.3 mg/dL), and bradycardia (heart rate <50 bpm detected by electrocardiogram) will be recorded and evaluated. The medication quantity will be determined by daily defined dose (DDD) calculated as per World Health Organization standard (the DDD is a system for exact quantification of drug amount and standardization to enable comparison across drug classes, eg, 1×DDD=150 mg irbesartan or 5 mg amlodipine).[18] The quality of life is assessed by the Bulpitt hypertension- specific questionnaire.[19] Two-dimensional echocardiography will be obtained by Artida Echocardiograph (Toshiba Medical Systems Corporation, Tokyo, Japan) and tend-diastolic left ventricular (LV) dimensions were used to calculate LV mass by an anatomically validated formula,[20] and subsequently normalized body height$^{2.7}$,[21] The caring physicians will remain blinded to the allocation by providing them with the measured BP values through a standardized report form without the knowledge of the used BP monitoring devices. Except patient reported outcome and adverse events, the investigators and participants are blinded to all the above outcome variables (which will be calculated at the end of the study), and assessment of LV mass will be conducted on side-by-side images by a technician blinded to allocation.

Data Analysis and Statistical Analyses

Based on data from our previous work,[22] sample size (84 participants per group)

was determined on the basis of noninferiority between 3 independent groups (α=0.05; β=0.20; standard deviation of ambulatory BP 11 mmHg; mean difference and non-inferior margin 5 mmHg, drop rate 10%).

We will test the normality of all parameters using the Shapiro–Wilk test. Categorical data are shown as proportions. Continuous data as means and standard deviations (SD) or as medium and interquartile ranges will be presented when appropriate.

Data will be analyzed on all patients who received the allocated strategy by intention-to-treat analysis if possible. For continuous variables of LV mass index, 24-hour ambulatory BP, heart rate, and quality of life, analysis will be undertaken using linear regression, with the dependent variable calculated as change over time. We will analyze DDD medication data recorded at all visits by using mixed regression models to account for repeated measures on individuals over time, with outcome variables log-transformed to correct heteroskedasticity where necessary.
The back-transformed means and confidence intervals are presented.
Recommendations on medication use at each visit were categorized as maintain, increase, decrease or cease.[14] A log-multinomial regression model will be used to assess the group differences for each of these 3 arms, with clustering on individuals to account for repeated measures over time. χ2 test will be used to determine the

relationship between categorical variables. Intra-class correlations and paired t-test are used to assess the agreements between different strategies. A data safety monitoring board will be convened to oversee the progress of the study conduct and data relating to safety issue.

Data Safety Monitoring

We have established a Data Safety Monitoring Board (DSMB) to monitor all aspects of the study. All issues related to participants' safety will be reported by the Medical Safety Officer to the independent DSMB, which will monitor data and oversee participant safety and will meet twice a year to monitor safety. They will also advise the research steering committee the study progress and performance, and make recommendations regarding the study continuation and protocol change. Efforts to early identify any major adverse outcomes of therapy will be made by the DSMB. The following is the possible safety events relating to the intervention: Serum sodium < =132 or >150 mEq/L; serum potassium <3.0 or >5.5 mEq/L; serum creatinine increase by at least 50% to a value >=1.5 mg/dL since the last study lab; heart rate <40; ECG complete heart block, or bradycardia <40 beart/min; injurious falls; syncope; any unexpected events for which the investigator believes that could be attributed to the intervention strategies. Serious adverse events are any adverse events that meet any of the following criteria: fatal or life-threatening, result in

significant or persistent disability, require or prolong hospitalization, and any events that investigators judge to represent significant hazards or harm to research.

Discussion

Rationale

The BP measurement is the clinical procedure of greatest importance given it serves as an imperative foundation in the management of hypertension, which is the most significant cardiovascular risk factor across the globe.[23] However, a substantial whitecoat effect, the difference between office and out-of-office BP, can be observed in the measurement process of office BP in routine clinical practice, which can make the adjustment of antihypertensive agents a challenging task.[24] Subsequently, home BP and uAOBP have been confirmed as successful strategies to eliminate the whitecoat effects. In addition, central BP has been shown to better conventional office BP in the prediction of cardiovascular risk[25] and may be a more cost-effective strategy in the diagnosis of hypertension.[26] In the era of evidence-based medicine, clinical trials are required to investigate the comparative effectiveness between these readily available BP monitoring strategies to inform clinical practice decisions.[27] Using the gold standard of BP monitoring, the ambulatory BP, as the primary endpoint,[28] we suggest home BP monitoring may be non-inferior to uAOBP and central BP monitoring as a guiding tool in the management of hypertension. Home BP is obtained by consecutive measurements and therefore is associated with a better accuracy and prognostic value than

conventional office BP. Moreover, home BP monitoring can be conducted in an easier way than uAOBP. If a comparable effectiveness could be demonstrated, it may have the potential to become the standard guiding procedure for hypertension.

Challenges in using office BP values to guide the clinical management of hypertension

Using conventional office BP in the management of hypertension is heavily influenced by the busy and hurry clinical environment. In a previous review article, it has been demonstrated that the routine office BP is substantially higher than research office BP, uAOBP, and daytime ambulatory BP.[29] Therefore, it could be risky and imprudent to titrate antihypertensive agents solely based on routine office BP. As such, many alternative strategies have been proposed to replace conventional office BP to guide the management of hypertension.[11 30-32] With the corresponding feasibility and effectiveness, home BP might be the strategy of choice to be implemented in the care of hypertensive subjects. However, its comparative effectiveness and safety in comparison with uAOBP and central BP monitoring have never been evaluated.

uAOBP: the best BP measuring technique?

Unattended AOBP, with its potential to eliminate whitecoat effect, has been adopted in SPRINT study.[3 33] One may partly attribute the success of SPRINT study to

the use of a more accurate BP measurement technique. It is therefore a promising technique to be used in routine clinical practice. However, in the practice of some clinical settings, it is probably unrealistic to implement this technique given its requirement of time, space, and the investment in the device cost. Without a randomized control trial comparing the effectiveness and safety between different BP monitoring strategies, it is difficult to make an evidence-based decision to guide the clinical management of hypertension.

Double blind versus open label design for the treatment strategies

We designed this study as a double-blind study for the clinical information will be provided for clinicians without the knowledge of the BP monitoring used for measure subjects' BP. The allocation concealment and blinding to patients, care givers, and outcome accessors will be rigorously kept avoiding possible placebo or performance bias. To our knowledge, it may be the first randomized controlled trial using the double-blind technique to evaluate the best BP monitoring strategy.

Blood pressure threshold

We adopt a common BP target based on the recommendation of the latest hypertension guideline for uAOBP and home BP.[6] Usually, central BP is lower than brachial BP. However, central BP device can be further classified into two types according to whether there is a preserved BP amplification, ie. Devices purports to

give an estimate of central BP relative to measured brachial BP (type I) or purports to estimate the intra-arterial central BP (type II).[34] We previously conducted a hypertension prevalence survey in the 2013–2016 National Nutrition and Health Survey in Taiwan.[35] In this national representative cohort, a type 2 central BP device is adopted to measure central BP. As shown in this study, comparable values of central and brachial SBP/DBP were noted. We therefore decided to use the same BP target for central BP monitoring to guide hypertension treatment.

Conclusion

The GYMNs trial is ongoing now and due to complete in 2020. The trial should be fully powered to test its primary hypotheses. It is the first robust RCT to evaluate the optimal guiding strategy for hypertension will help define which BP monitoring is the most effective strategy to guide the clinical management of hypertension. Whatever the outcome, the findings of GYMNs are likely to influence future international guidelines for the choice of BP monitoring strategy in routine clinical practice in the care of hypertensive subjects.

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Conflict of interest disclosures:

Microlife Co., Ltd., and National Yang-Ming University have signed a contract for transfer of the noninvasive central blood pressure technique. The contract of technology transfer includes research funding for conducting studies validating this technique.

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Table 1 Study plan

Visit number	Screening	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Day	-1~-14	0	30 (±7)	60 (±7)	90 (±7)	180 (±7)	270 (±7)	360 (±7)
Visit timing			1M	2M	3M	6M	9M	12M
Site visits	√	√	√	√	√	√	√	√
Sign Informed Consent Form	√							
Medical history	√							
Inclusion/Exclusion Criteria	√	√						
Randomization		√						
Concomitant antihypertensive drugs	√	√	√	√	√	√	√	√
Medical record	√	√	√	√	√	√	√	√
Adverse Event (related study)		√	√	√	√	√	√	√
Height	√							
Weight	√	√	√	√	√	√	√	√
Physical examination	√	√	√	√	√	√	√	√
echocardiography		√						√
Blood test	√							√
Hemodynamic examination		√						√
ABPM		√			√			√
uAOBP	√	√	√	√	√	√	√	√
Home BP		√	√	√	√	√	√	√
Central BP		√	√	√	√	√	√	√
Questionnaire		√						√

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使用不同測量血壓方式對於血壓控制之影響-隨機對照研究

研究機構：臺北榮民總醫院

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本計畫二十四小時緊急聯絡人及電話：鄭浩民主任 0952460009

受試者姓名：
性別：　　出生日期：
病歷號碼：
通訊地址：
聯絡電話：
受試者緊急聯絡人：　　電話：
通訊地址：

法定代理人/監護人/輔助人或有同意權人姓名：
與受試者關係：
性別：　　出生日期：
身分證字號：
通訊地址：
聯絡電話：

1. 研究背景簡介：

我們希望邀請您參加一項高血壓治療的學術研究，本研究計畫不涉及藥品、醫療技術、醫療器材。為了幫助您進行決定，您應瞭解本研究以及和您有關係的事情，這個過程稱為「知情同意」，請抽空仔細閱讀以下資訊，如有任何不清楚的地方，請向研究醫師提問，如果您決定參加，您將必須簽署本同意書，您將獲得一份受試者同意書副本，正本將保留在研究單位。本研究的經費來源為主持人自籌及衛生福利部部分贊助。

高血壓是重要的心血管危險因子之一，過去有許多文獻顯示治療高血壓能顯著地降低中風及心肌梗塞的風險。一般傳統的血壓量測，主要是在醫院門診進行，可能產生白袍現象，獲得偏高的血壓數值。因此，目前心臟學會及高血壓學會推薦居家血壓量測，再將血壓記錄帶回給醫師評估，此外中央動脈血壓也已有文獻顯示與周邊上臂血壓有顯著的不同。然而，究竟哪一種血壓量測方法才能幫助醫師及病患進行良好的血壓控制，目前仍不清楚。因此我們將透過進行這個研究來探討這個重要的臨床課題。本研究將在臺北榮民總醫院進行，預計納入 252 位受試者，

每位受試者預計進行 8 次的研究訪視(為期約 13 個月)。

2. 研究目的

此隨機對照研究將病患依血壓量測方式，隨機分配(電腦抽籤)至門診血壓量測組、居家血壓量測組及中央動脈血壓量測組。醫師將透過相關組別之血壓量測的數值，進行高血壓藥物的調整。醫師與病患將不知道病患所分配的血壓量測方式，我們將比較三組 24 小時血壓的平均血壓數值，了解三種策略對於血壓控制的效果。本研究預計於篩選期及第 12 個月採集血液(每次約 8 c.c)與尿液(每次約 10 c.c.)檢體。

3. 研究之主要納入與排除條件

主要納入條件：

- 年齡 20 至 90 歲。
- 未懷孕。
- 新診斷高血壓或是服用 1 種或 2 種高血壓藥物但血壓仍控制不佳未達 130/80 mmHg 需要調整治療血壓藥物的病患。

主要排除條件：

- 複雜性高血壓與頑固性高血壓患者。
- 服藥遵從性不佳者。
- 無法進行居家血壓量測者。
- 先天性多囊腎病史。
- 患有心衰竭(篩選前最近一次紀錄，左心室射出分率< 40%)、慢性腎臟疾病(篩選期腎絲球過濾率< 30 mL/min/1.73m2)。
- 篩選期無人自動化診療室血壓量測>180/100 mm Hg。
- 左右手血壓差距超過 5 mmHg 者。

4. 研究方法及相關配合檢驗

簽署這份知情同意書後即開始參與本研究，直到完成最後規劃的研究回診。本研究將會收集您的基本資料、病史等，並且進行篩選訪視，符合研究條件的受試者將隨機分配(電腦抽籤)至(1)無人自動化診療室血壓量測組、(2)中央動脈血壓量測組、或(3)居家血壓量測組，隨機分配的比例為 1:1:1，被分配任一組的機率分別為 1/3。您需要接受前述三種血壓量測方式，研究人員再依照電腦分配的組別，抄錄分派組別的血壓值

交給醫師調藥。此研究為雙盲試驗，您和您的研究醫師不會知道您被分配的結果，研究期間您及研究醫師將維持盲性。被隨機分配的受試者之後將會進行第 1 個月、第 2 個月、第 3 個月、第 6 個月、第 9 個月及第 12 個月的研究訪視，您參與本研究的總期間將持續約 13 個月，包含小於 2 週的篩選期（這些期間的研究回診程序及特殊研究程序說明如下）。

研究回診程序

每次研究回診預計花費 40 至 60 分鐘。

研究回診	篩選期	訪視 1	訪視 2	訪視 3	訪視 4	訪視 5	訪視 6	訪視 7
	-1 天~-14 天	第 0 天	30 天±7 天	60 天±7 天	90 天±7 天	180 天±7 天	270 天±7 天	360 天±7 天
			1 個月	2 個月	3 個月	6 個月	9 個月	12 個月
門診訪視	√	√	√	√	√	√	√	√
簽署同意書	√							
病史詢問	√							
納入/排除條件	√	√						
隨機分派		√						
服用血壓藥物紀錄	√	√	√	√	√	√	√	√
病歷紀錄	√	√	√	√	√	√	√	√
與研究相關不良事件紀錄		√	√	√	√	√	√	√
身高	√							
體重	√	√	√	√	√	√	√	√
身體評估	√	√	√	√	√	√	√	√
心臟超音波檢查		√						√
血液與尿液檢測	√							√
血流動力學檢測		√						√
24 小時血壓量測 ABPM		√			√			√
無人自動化診療室血壓量測 uAOBP	√	√	√	√	√	√	√	√

居家血壓量測 Home BP		√	√	√	√	√	√	√
中央動脈血壓量測 Central BP		√	√	√	√	√	√	√
問卷		√						√

特殊研究程序

- 血壓量測

  24 小時血壓量測、無人自動化診療室血壓量測、居家血壓量測、中央動脈血壓量測皆非侵入性檢查，研究人員將協助及指導您完成量測。

  (1) 24 小時血壓量測：研究人員於訪視 1、訪視 4 與訪視 7 訪視前一日提供可攜式血壓計，請您帶回家，您回家後連續 24 小時配戴血壓計進行血壓的量測，血壓計會自動紀錄 24 小時的血壓值，再請您將血壓計攜回，交給研究人員。

  (2) 無人自動化診療室血壓量測：研究人員帶您至診療室靜坐五分鐘後，在沒有醫護人員監督下使用自動電子血壓計進行三次血壓的測量，每次間隔一分鐘，並算出血壓平均值。

  (3) 居家血壓量測：研究人員於每次訪視日會提供居家用血壓計，請您帶回家，請您在研究預定下次訪視日之前連續七天的早上和晚上，進行血壓的量測，血壓計會自動記錄血壓量測時間與結果。請您在預定訪視日將血壓計攜回，交給研究人員。

  (4) 中央動脈血壓量測：研究人員帶您至至診療室靜坐五分鐘後，使用中央動脈血壓計進行血壓的測量。

- 心臟超音波檢查

  是一種非侵入性的檢查，我們只需將超音波探頭置於病患胸前即可獲得心臟結構和功能之測量數據，是心臟科常規的檢查，可提供我們治療心臟疾病之重要參考數據。

- 血液與尿液檢測

  於篩選期及第 12 個月檢測，每次血液(每次約 8 c.c)與尿液(每次約 10 c.c.)。

- 血流動力學檢查

  是一種非侵襲性的檢查，只需要將四個量測血壓的壓脈帶和四個心電

圖電極貼片固定於四肢，並將一個心音紀錄器置於胸前，另外兩個高傳真探頭放在頸部和鼠蹊部，即可方便快速地紀錄心電圖、心音圖，以及量測心四肢的血壓、動脈的波型和脈波傳導速度。

- 高血壓藥物的調整

  配合臨床常規進行，研究醫師將依據量測的血壓紀錄調整高血壓藥物。

5. 可能發生的副作用、發生率及處理方法：

本研究計畫不涉及藥品、醫療技術、醫療器材，因此參與本研究沒有可預期的副作用，而研究程序相關的風險，如下：

抽血

抽血部位出現瘀傷、出血、感染，以及罕見的昏厥和/或神經損傷造成的不適。

心電圖檢查

檢測貼片貼在您身體上的不同部位，心電圖檢查不會導致疼痛或不適；然而在移除檢測貼片時可能會對皮膚造成些許刺激。

血流動力學檢查

前臂會有如量血壓時般短暫的脹脹感覺。

心臟超音波檢查

心臟超音波探頭會壓在身上，可能會有些壓迫感。

問卷

若因詢問問卷時間過長，讓您身心感到不適，您可要求研究人員隨時終止詢問。

個人資訊收集

您的個人資訊有可能外洩，但風險較低；然而，我們已經採取步驟來確保不會發生這種情況，對於就業/保險方面—參與本研究不會有直接的風險。但若他人(例如您的保險公司或雇主)無意中得知您參與研究的結果，或許會產生對您不利的影響。但此風險極低，因為您的資料會被以極機密保存。任何的研究報告中將不會有您的個人資料，此研究的結果亦不會與研究資料庫連結。因此，透過這些適當的處理，我們可以盡可能的降低這些風險對您的影響。

6. 其他可能之治療方式及說明

本研究計畫不涉及藥品、醫療技術、醫療器材，您的替代方案是不參加本研究。

7. 研究預期效果

本研究所收集的資訊可能增進對您疾病的瞭解，此外本研究的結果可能會提供重要資訊給醫護專業人員，了解哪種血壓量測方式能幫助臨床醫師及病患進行良好的血壓控制。

8. 研究進行中受試者之禁忌、限制與應配合之事項

本研究無禁忌及限制事項，需配合研究定期回診。

9. 機密性

臺北榮民總醫院將依法把任何可辨識您的身分之記錄與您的個人隱私資料視為機密來處理，不會公開。研究人員將以一個研究代碼代表您的身分，此代碼不會顯示您的姓名、國民身分證統一編號、住址等可識別資料。如果發表研究結果，您的身分仍將保密。您亦瞭解若簽署同意書即同意您的原始醫療紀錄可直接受監測者、稽核者、臺北榮民總醫院人體試驗委員會及主管機關檢閱，以確保研究過程與數據符合相關法律及法規要求，上述人員並承諾絕不違反您的身分之機密性。除了上述機構依法有權檢視外，我們會小心維護您的隱私。

10.損害補償與保險

- 如依本研究所訂研究計畫，因而發生不良反應或傷害，由臺北榮民總醫院負補償責任。但本受試者同意書上所記載之可預期不良反應，將不予補償。
- 如依本研究所訂臨床研究計畫，因而發生不良反應或損害，臺北榮民總醫院願意提供專業醫療照顧及醫療諮詢。您不必負擔治療不良反應或損害之必要醫療費用。
- 除前二項補償及醫療照顧外，本研究不提供其他形式之賠償或補償。若您不願意接受這樣的風險，請勿參加研究。
- 您不會因為簽署本同意書，而喪失在法律上的任何權利。
- 本研究未投保責任保險。

11.誰可以使用您的檢體及資料

依「人體研究法」規定，唯有計畫主持人、共同/協同主持人及本計畫含括之人員可於研究進行期間依本研究所訂研究計畫使用您的研究資料(含檢體)，如於研究結束後仍需使用，將依法請您另簽一份同意書。

12.研究結束後檢體及資料處理和儲存方法

I. 檢體及剩餘檢體之保存與使用

(1) 檢體之保存與使用

為研究所需，我們所蒐集您的檢體，將依本研究計畫使用，檢體將保存於臺北榮民總醫院，直至 20 年保存期限屆滿，我們將依法銷毀。為了保護您的個人隱私，我們將以一個研究編號來代替您的名字及相關個人資料，以確認您的檢體及與相關資料受到完整保密。如果您對檢體的使用有疑慮，或您有任何想要銷毀檢體的需求，請立即與我們聯絡(臺北榮民總醫院鄭浩民主任，電話：(02) 28771746)，以協助您解決檢體在研究使用上的任何爭議。

(2) 剩餘檢體之再利用

您的生物檢體將會以專屬號碼進行編碼並在臺北榮民總醫院的控管下儲存最長 20 年。

所有新的研究計畫都要再經由人體試驗委員會審議通過，人體試驗委員會若認定新的研究超出您同意的範圍，將要求我們重新得到您的同意。

是否同意剩餘檢體保留提供未來高血壓研究之用（請說明特定疾病範圍，並以試驗疾病為宜），並授權人體試驗委員會會審議是否需要再取得您的同意**(擇一)**

☐ 不同意保存我的剩餘檢體，研究結束後請銷毀

☐ 同意以非去連結之方式保存我的剩餘檢體，逾越原同意使用範圍時，需再次得到我的同意才可使用我的檢體進行新的研究

☐ 同意以去連結之方式保存我的剩餘檢體(去連結是指將您的檢體及資料編碼後，會銷毀這個編碼與您個人可辨識資料(如姓名、身分證字號、病歷號等)的連結，使永遠無法經由編碼辨識或連結到您的個人資訊。因此若您選擇以去連結的方式處理及保存剩餘檢體，您未來無法要求銷毀檢體，且使用檢體進行其他研究時，亦無法再次取得您的同意，因為一旦去連結後，

就無法辨識出哪一個檢體是您當初所提供。）

II. 檢體及剩餘檢體之部分類型

(1) 一般生化、血液檢驗檢體

在研究期間會將您的檢體送往臺北榮民總醫院分析，臺北榮民總醫院會在分析後立即將分析結果提供給研究單位。完成研究後，若有剩餘檢體，將保存於臺北榮民總醫院，最長將保存 20 年。

(2) 生物標記檢體、尿液檢體

在研究期間會將您的檢體送往臺北榮民總醫院分析，臺北榮民總醫院會在分析後立即將分析結果提供給研究單位。完成研究後，若有剩餘檢體，將保存於臺北榮民總醫院，最長將保存 20 年。

III. 個人資料

在研究期間依據研究計畫類型與您所授權的內容，我們將會蒐集與您有關的病歷資料、醫療記錄、問卷等資料與資訊，並以一個研究編號來代替您的名字及相關個人資料。前述資料與資訊若為紙本型式，將會與本同意書分開存放於研究機構之上鎖櫃中；若為電子方式儲存或建檔以供統計與分析之用，將會存放於設有密碼與適當防毒軟體之專屬電腦內。研究結束後，問卷資料會以維護個資的方式匿名保存，研究資料會保存在研究人員的電腦，以匿名的方式處理，如果受試者不希望自己的資料被使用時，研究人員將銷毀相關資料。

13.研究之退出與中止及其檢體及資料處理方法

您可自由決定是否參加本研究；研究過程中也可隨時撤銷同意，退出研究，不需任何理由，且不會引起任何不愉快或影響其日後醫師對您的醫療照顧。

當研究執行中有重要的新資訊(指和您的權益相關或是影響您繼續參與意願)，會通知您並進一步說明，請您重新思考是否繼續參加，您可自由決定，不會引起任何不愉快或影響其日後醫師對您的醫療照顧。研究主持人亦可能於必要時(例如：您參與研究後發現血壓控制不穩定，發生中風、心肌梗塞或危急性之血壓不穩定等高血壓急症等。)中止該研究之進行。但您的醫師對您的醫療照顧將不會造成影響。

當您退出本研究或主持人判斷您不適合繼續參與本研究時，在退出前已得到的資料將被保留，不會移除。在退出後您可選擇如何處理您先前提供的檢體，與決定是否同意研究主持人或贊助廠商繼續收集您的資料。

(1) 對我先前所提供的檢體(**擇一**)

□我同意繼續授權本研究使用於本研究疾病相關的研究。逾越原書面同意使用範圍時，需再次經過我同意。

□不同意繼續授權本研究使用，但為確保已完成檢查之準確性，同意研究相關檢體可由實驗室進行再次確認後銷毀。

□不同意繼續授權本研究使用，請自我退出日起銷毀我之前的本研究相關檢體。

(2) 退出後讓研究主持人繼續收集我的資料，例如經由我的病歷記載取得後續醫療過程、實驗室檢查結果。繼續收集資料期間，仍會維護您的隱私和個人資料的機密性。(**擇一**)

□同意收集。

□不同意本研究繼續收集或檢視我的資料。

14.如本計畫研究成果獲得學術文獻發表、智慧財產及實質效益時，臺北榮民總醫院將依法作為從事疾病診斷、預防、治療及研究等醫學用途。

15.受試者權利與義務

(1) 參加本研究您不須繳交任何費用。對於研究計畫書規定的篩選期、第 12 個月(訪視 7)回診，我們將會提供新台幣 500 元作為補助。

(2) 本研究不在全民健康保險之給付範圍。所有研究有關費用均由本計畫負擔。

(3) 研究過程中，與您的健康或是疾病有關，可能影響您繼續接受研究意願的任何重大發現，都將即時提供給您。如果您決定退出，醫師會安排您繼續接受醫療照護。如果您決定繼續參加研究，可能需要簽署一份更新版的同意書。

(4) 若研究結束後 1 年內，發現有非預期且直接影響您的安全疑慮，亦將通知您。

(5) 如果您在研究過程中對研究工作性質產生疑問，對身為患者之權利有意見或懷疑因參與研究而受害時，可與本院之人體試驗委員會聯絡請求諮詢，其電話號碼為：(02)2875-7384。

(6) 為進行研究工作，您必須接受主持人及研究團隊的照顧。如果您現在或於研究期間有任何問題或狀況，請不必客氣，可與在臺北榮民總醫院實證醫學中心的鄭浩民主任聯絡(24 小時聯繫電話：0952460009)。

(7) 本同意書一式 2 份，主持人已將同意書副本交給您，並已完整說明本研究之性質與目的。鄭浩民主任及研究團隊已回答您有關研究的問題。

16.簽名

（一）主要主持人、或協同主持人保證我本人或我的研究團隊中的一位成員（已獲授權進行本步驟的代表），已經對上述人士解釋過本研究，包括本研究的目的、程序與參加本研究可能的相關危險性和效益，以及目前可行的替代治療。所有被受試者提出之疑問，均已予以答覆。

主要主持人／共同主持人/協同主持人：_____(簽名)

日期：____年____月____日(請務必填寫)

研究說明者：_____(簽名)

研究說明者與研究之關係：_____

日期：____年____月____日(請務必填寫)

（二）受試者已詳細瞭解上述研究方法及其所可能產生的危險與利益，有關本研究計畫的疑問，業經計畫主持人詳細予以解釋。本人同意接受為臨床研究計畫的自願受試者。

受試者：_____(簽名)

日期：____年____月____日(請務必填寫)

註 1. 本受試者同意書適用範圍為年滿二十歲以上之成年人，且受試者必須由其本人簽名，並且載明日期始得生效。

註 2. 若受試者無法閱讀上述內容，而係經由研究人員口述說明，需有一名法定代理人、監護人/輔助人或有同意權人在場

法定代理人 1：_____(簽名)

與受試者之關係：_____(簽名)

日期：____年____月____日(請務必填寫)

法定代理人 2：_____(簽名)

與受試者之關係：_____(簽名)

日期：____年____月____日(請務必填寫)

註 2. 未滿二十歲之受試者或受法律之監護宣告者，須由法定代理人簽名始生效。

註 3. 受試者為無行為能力(未滿七歲之未成年人者或受監護宣告之人)，由法定代理人為之；受監護宣告之人，由監護人擔任其法定代理人。

註 4. 受試者為限制行為能力者(七歲以上之未成年人)，應得其本人及法定代理人之同意。

註 5. 年滿七歲以上未滿十二歲的受試者：須另加一份贊同同意書，請用圖案表示或注音，取得其贊同。

監護人/輔助人或有同意權人 1：_____(簽名)

與受試者之關係：_____(簽名)

日期：____年____月____日(請務必填寫)

監護人/輔助人或有同意權人 2：_____(簽名)

與受試者之關係：_____(簽名)

日期：____年____月____日(請務必填寫)

註 6. 受試者因精神障礙或其他心智缺陷，致其為意思表示或受意思表示，或辨識其意思表示效果之能力，顯有不足，而受法院之輔助宣告者，應得其本人及法定代理人或輔助人之同意。

註 7. 受試者雖非無行為能力或限制行為能力者，但因意識混亂或有精神與智能障礙等，而無法進行有效溝通和判斷時，由有同意權之人為之。前項有同意權人為配偶及同居之親屬。其順序如下，一、配偶。二、成年子女。三、父母。四、兄弟姊妹。五、祖父母。依前項關係人所為之書面同意，其書面同意，得以一人行之；關係人意思表示不一致時，依前項各款先後定其順序。前項同一順序

之人，以親等近者為先，親等同者，以同居親屬為先，無同居親屬者，以年長者為先。

（三）受試者、法定代理人、監護人/輔助人或有同意權之人皆無法閱讀時，應由見證人在場參與所有有關受試者同意之討論。並確定受試者、法定代理人、監護人/輔助人或有同意權之人之同意完全出於其自由意願後，應於受試者同意書簽名並載明日期。

茲證明主要主持人、或協同主持人已完整地向受試者或其法定代理人、監護人/輔助人或有同意權之人解釋本研究的內容。

見證人 1：_____(簽名)

見證人 1 身分：_____(簽名)

身分證字號：_____

日期：____年____月____日(請務必填寫)

聯絡電話：_____

通訊地址：_____

見證人 2：_____(簽名)

見證人 2 身分：_____(簽名)

身分證字號：_____

日期：____年____月____日(請務必填寫)

聯絡電話：_____

通訊地址：_____

註 8. 研究/試驗相關人員不得為見證人。

註 9. 若意識清楚，但無法親自簽具者且無親屬或關係人在場，得以按指印代替簽名，惟應有二名見證人。