**EFFECT OF ANGIOTENSIN RECEPTOR BLOCKERS ON BOOD PRESSURE CONTROL AMONG EUVOLEMIC HYPERTENSIVE HEMODIALYSIS PATIENTS: A RANDOMIZED CONTROLLED TRIAL**

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**Study Protocols**

**Research Title**

Effect of Angiotensin Receptor Blockers on Bood Pressure Control Among Euvolemic Hypertensive Hemodialysis Patients: A Randomized Controlled Trial

**Short title**

Angiotensin Receptor Blockers on Management of euvolumic but hypertensive hemodialysis patients

**Principle investigator**

Dr Amer Hayat Khan

(Senior lecturer Discipline of clinical pharmacy, USM)

Staff number: 0949/11

**Nephrologists**

Dr Azreen Syazril Adnan (Consultant Nephrologists & Physician)

(Consultant Nephrologists & Physician, Discipline of Medicine, USM)

Staff number: 0866/10

**Cardiologist**

Dr.Hady, MMed

Lecturer and Physician of Medical Department (cardiology), Hospital USM

Staff number: 0675/13

**Researcher**

Raja Ahsan Aftab

(PhD candidate, Discipline of clinical pharmacy, USM)

Matirc Card : PFD-0022/14(R)

**Study Site**

Hospital Universiti Sains Malaysia (HUSM), Kelantan, Malaysia

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# List of Abbreviations

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|  | **Abbreviations**  |
| ESRD | End Stage Renal Disease |
| RAAS | Renin angiotensin aldosterone system |
| ARB | Angiotensin receptor blocker  |
| HTN | Hypertension  |
| BCM | Body composition monitor |
| ACE inhibitors | Angiotensin converting enzyme inhibitors |
| RCT | Randomized control trial |
| HD | Hemodialysis  |
| PD | Peritoneal dialysis  |
| HUSM | Hospital Universiti Sains Malaysia |
| ECG | Electro cardiogram |
| CP | Complete picture  |

# Summary

Patients with End Stage Renal Disease (ESRD) requires lifelong fluid replacement therapy or renal transplant. **Almost 60-90 % hemodialysis patients are hypertensive.** Initial studies aimed at elucidating the pathophysiology of hypertension in this category of patients concluded that 90% of hemodialysis hypertension cases resulted from sodium and volume overload (volume-dependent), while the majority of the remaining cases have elevated renin activity (rennin dependent), leading to renin dependent high blood pressure.

Since there is a constant volume variation during dialysis session, there is a strong possibility for activation of Renin angiotensin aldosterone system (RAAS) during dialysis. This activation of RAAS would lead to vasoconstriction of arteries and causes a rise in blood pressure even the patient hydration status is normal. Hence these patients at the end of dialysis session are euvolumic but still hypertensive**.** Body composition monitor (BCM) helps estimate patient hydration status accurately which previously was estimated by clinical findings. Keeping in view the importance of RAAS system, the current study is designed as randomized control trial to note the effect of ARB on blood pressure control among euvolumic but hypertensive patients. The study is a two phase study, were phase one or the pre-screening phase involves identification of post dialysis euvolumic patients via BCM. Phase two involves randomization of identified euvolumic hypertensive patients into two study arms, the ARB arm (interventional group) or NO ARB (control group) arm. Patients after undergoing washout period will be given medication with respect to their study arm**.** At the start of RCT patients will undergo examination from a nephrologists and a cardiologist to note initial cardiovascular complications, this examination will be repeated at four month period and at the conclusion of study. All pre, intra and post dialytic data for eight months will be recorded on a validated data collection form. The primary end point of study would be achieving targeted blood pressure of <140/90 mmHg and maintaining for three weeks. The secondary point will be all cause of mortality

 The study should provide interesting information regarding role of ARB in managing euvolumic hypertensive post dialysis population

# SECTION I

## Background

A patient is determined to have ESRD when he or she requires replacement therapy, including dialysis or kidney transplantation. In 2009, more than 570,000 people in the United States were classified as having end-stage renal disease (ESRD), including nearly 400,000 dialysis patients and over 17,000 transplant recipients [1,2].  The rise in incidence of ESRD is attributed to an aging populace and increases in hypertension (HTN), diabetes, and obesity within the U.S. population. ESRD is associated with a host of complications including electrolyte imbalances, mineral and bone disorders, [anemia](http://emedicine.medscape.com/article/198475-overview?src=wgt_edit_news_lsm&lc=int_mb_1001), dyslipidemia, and HTN [3]

After rising steadily from 1980 to 2001, the incident rate of ESRD **levelled off to 350 million worldwide. In Malaysia, 21st Malaysian dialysis and transplant registry 2013 report that 5491, new hemodialysis cases were registered representing an acceptance rate of 15 per million population while new peritoneal dialysis cases totalled 731, representing an acceptance rate of 25 per million population. The total number HD & PD patients in 2013 increased to 28,822 and 2815 respectively, giving a prevalence rate of 970 per million populations respectively. In last decade, both the acceptance and prevalence rate had increased by almost two-fold. Geographically, the dialysis rate exceeded 100 per million population for all states in Malaysia by the year 2013 with highest rates reported in Pulau Pinang (303 pmp) and least in Perlis (104 pmp). Over the last 10 years, the ratio of male to female incident & prevalent dialysis patients had remained the same about 55-45% [4].**

## ****Post dialysis and hypertension****

**Almost 60-90 % hemodialysis patients are hypertensive.** Initial studies aimed at elucidating the pathophysiology of hypertension in this category of patients concluded that 90% of cases resulted from sodium and volume overload (volume-dependent), while the majority of the remaining had elevated renin activity (renindependent), resulting in a rise in renin and blood pressure during hemodialysis as fluid is removed [5].

**Figure 1: Pathogenesis of hypertension in Dialysis patients**



In brief, the mechanisms of hypertension are difficult to unravel in patients on hemodialysis given their intricacy. The heterogeneity of the dialysis population results in probable significant overlap of the above-mentioned causes. However, a majority consensus agrees that the most predominant factor is related to expanded extracellular volume.

## Renin angiotension system in management of post dialysis hypertension

The renin-angiotensin-aldosterone system (RAAS) is a signaling pathway responsible for regulating the body's blood pressure. Stimulated by low blood pressure or certain nerve impulses (e.g. in stressful situations), the kidneys release an enzyme called renin. This triggers a signal transduction pathway: renin splits the protein angiotensinogen, producing angiotensin I. This is converted by another enzyme, the angiotensin-converting enzyme (ACE), into angiotensin II [7].

Angiotensin II not only causes blood vessels to narrow (vasoconstriction), it also simultaneously stimulates the secretion of the water-retaining hormone vasopressin (also called AVP) in the pituitary gland (hypophysis) as well as the release of adrenaline, noradrenaline and aldosterone in the adrenal gland .

Whereas adrenaline and noradrenaline enhance vasoconstriction, aldosterone influences the filtration function of the kidneys. The kidneys retain more sodium and water in the body and excrete more potassium. The vasopressin from the pituitary gland prevents the excretion of water without affecting the electrolytes sodium and potassium.

In this way, the overall volume of blood in the body is increased: more blood is pumped through constricted arteries, which increases the pressure exerted on the artery walls the blood pressure. Since there is a constant volume variation during dialysis, there is a strong possibility for activation of RAAS system during dialysis. This causes vasoconstriction of arteries and causes a rise in blood pressure even the patient hydration status is normal [8].

**Figure 2 shows a schematic diagram to for RAAS activation and its effects on different organ system**



## Euvolumic hypertension

Since there is a constant volume variation during dialysis, there is a strong possibility for activation of RAAS system during dialysis. This causes vasoconstriction of arteries and causes a rise in blood pressure even the patient hydration status is normal. Hence these patients are euvolumic but still hypertensive.

## Role of Angiotensin Converting Enzyme Inhibitors and Angiotensin receptor blocker in Activation of Renin Angiotensin Aldosterone System

### Angiotensin Converting Enzyme Inhibitors (ACE Inhibitors)

ACE inhibitors produce vasodilation by inhibiting the formation of angiotensin II. This vasoconstrictor is formed by the proteolytic action of renin (released by the kidneys) acting on circulating angiotensinogen to form angiotensin I. Angiotensin I is then converted to angiotensin II by angiotensin converting enzyme [9].

ACE also breaks down bradykinin (a vasodilator substance). Therefore, ACE inhibitors, by blocking the breakdown of bradykinin, increase bradykinin levels, which can contribute to the vasodilator action of ACE inhibitors. The increase in bradykinin is also believed to be responsible for a troublesome side effect of ACE inhibitors, namely, a dry cough.

ACE inhibitors are effective in the treatment of primary [hypertension](http://cvpharmacology.com/clinical%20topics/hypertension) and hypertension caused by renal artery stenosis, which causes renin-dependent hypertension owing to the increased release of renin by the kidneys. Reducing angiotensin II formation leads to arterial and venous dilation, which reduces arterial and venous pressures. By reducing the effects of angiotensin II on the kidney, ACE inhibitors cause [natriuresis and diuresis](http://cvpharmacology.com/diuretic/diuretics), which decreases blood volume and cardiac output, thereby lowering arterial pressure [10].

ACE inhibitors have the following actions:

* Dilate arteries and veins by blocking angiotensin II formation and inhibiting bradykinin metabolism. This vasodilation reduces arterial pressure, [preload](http://cvphysiology.com/Cardiac%20Function/CF007.htm) and [after load](http://cvphysiology.com/Cardiac%20Function/CF008.htm) on the heart.
* Down regulate sympathetic adrenergic activity by blocking the facilitating effects of angiotensin II on sympathetic nerve release and reuptake of norepinephrine.
* Promote renal excretion of sodium and water ([natriuretic](http://cvpharmacology.com/diuretic/natriuretics) and [diuretic](http://cvpharmacology.com/diuretic/diuretics) effects) by blocking the effects of angiotensin II in the kidney and by blocking angiotensin II stimulation of [aldosterone](http://cvpharmacology.com/diuretic/diuretics) secretion. This reduces [blood volume](http://cvphysiology.com/Blood%20Pressure/BP025.htm), venous pressure and arterial pressure.
* Inhibit cardiac and vascular remodeling associated with chronic [hypertension](http://cvpharmacology.com/clinical%20topics/hypertension), [heart failure](http://cvpharmacology.com/clinical%20topics/heart%20failure), and [myocardial infarction](http://cvpharmacology.com/clinical%20topics/myocardial%20infarction).

### Angiotensin receptor blocker (ARB)

ARBs are receptor antagonists that block type 1 angiotensin II (AT1) receptors on bloods vessels and other tissues such as the heart. These receptors are coupled to the [Gq-protein and IP3 signal transduction pathway](http://cvphysiology.com/Blood%20Pressure/BP026.htm) that stimulates vascular smooth muscle contraction. Because ARBs do not inhibit ACE, they do not cause an increase in bradykinin, which contributes to the vasodilation produced by ACE inhibitors and also some of the side effects of ACE inhibitors (cough and angioedema) [11].

ARBs have the following actions, which are very similar to ACE inhibitors:

* Dilate arteries and veins and thereby reduce arterial pressure and [preload](http://cvphysiology.com/Cardiac%20Function/CF007.htm) and [after load](http://cvphysiology.com/Cardiac%20Function/CF008.htm) on the heart.
* Down regulate sympathetic adrenergic activity by blocking the effects of angiotensin II on sympathetic nerve release and reuptake of norepinephrine.
* Promote renal excretion of sodium and water ([natriuretic](http://cvpharmacology.com/diuretic/natriuretics) and [diuretic](http://cvpharmacology.com/diuretic/diuretics) effects) by blocking the effects of angiotensin II in the kidney and by blocking angiotensin II stimulation of [aldosterone](http://cvpharmacology.com/diuretic/diuretics) secretion.
* Inhibit cardiac and vascular remodeling associated with chronic [hypertension](http://cvpharmacology.com/clinical%20topics/hypertension), [heart failure](http://cvpharmacology.com/clinical%20topics/heart%20failure), and [myocardial infarction](http://cvpharmacology.com/clinical%20topics/myocardial%20infarction)

**Figure 3 summarizes the action of ACE inhibitors and ARB on inhibition of RAAS system**



**Literature review**

## Literature review

Cardiovascular disease is the leading cause of mortality in patients with kidney failure treated with hemodialysis (HD). Although angiotensin receptor blockers (ARBs) reduce cardiovascular disease (CVD) events in patients with diabetes and chronic kidney disease, their effect in patients with kidney failure on HD therapy is not known. For this purpose a Open-labeled randomized trial was carried out among hemodialysis patients was carried out to assess the cardiovascular changes with the use of ARBs. Patients aged 30 to 80 years receiving HD 2 to 3 times weekly for 1 to 5 years at 5 university-afﬁliated dialysis centers were recruited for the study. Treatment with ARBs (valsartan, candesartan, and losartan) versus without ARBs after stratiﬁcation by sex, age, systolic blood pressure, and diabetes was carried out. The primary end point is the development of fatal and nonfatal CVD events, deﬁned as the composite of CVD death, myocardial infarction, stroke, congestive heart failure, coronary artery bypass grafting, or percutaneous coronary intervention. The secondary end point is all-cause death.A total of366 subjects initially were randomly assigned to an ARB or no ARB (control), but after a run-in phase, 180 were retained in each group. Mean age was 60 years, 59% were men, 51% had diabetes, and mean predialysis systolic blood pressure was 154 mm Hg. There were 93 fatal or nonfatal CVD events (52%); 34 (19%) in the ARB group and 59 (33%) in the non-ARB group. After adjustment for age, sex, diabetes, systolic blood pressure, and center, treatment with an ARB was independently associated with reduced fatal and nonfatal CVD events (hazard ratio, 0.51; 95% conﬁdence interval, 0.33 to 0.79; ***P***\_0.002). There were 63 deaths (35%); 25 (14%) in the ARB group and 38 (21%) in the non-ARB group. After adjustment, all-cause mortality differed between the 2 groups (hazard ratio, 0.64; 95% conﬁdence interval, 0.39 to 1.06; ***P*** \_0.1). Because of the small sample size of this trial, the large effect may be a spurious ﬁnding. Use of an open-label design and 3 different agents in the ARB group might have inﬂuenced results. Use of an ARB may be effective in reducing nonfatal CVD events in patients undergoing long-term HD. A larger study is required to conﬁrm these results [12]

Treatment of hypertension in hemodialysis (HD) patients is characterised by lack of evidence for both the blood pressure (BP) target goal and the recommended drug class to use. Telmisartan, an Angiotensin receptor blocker (ARB) that is metabolised in the liver and not excreted via HD extracorporeal circuit might be particularly suitable for HD patients. We designed and conducted a randomised, placebo-controlled, double-blind and cross-over trial for treatment of dialysis– associated hypertension with telmisartan 80 mg once daily or placebo on top of standard antihypertensive treatment excluding other Renin-Angiotensin-System (RAS) blockers. In 29 patients after randomization we analysed BP after a treatment period of 8 weeks, while 13 started with telmisartan and 16 with placebo; after 8 weeks 11 continued with telmisartan and 12 with placebo after cross-over, respectively. Patients exhibited a significant reduction of systolic pre-HD BP from 141.9621.8 before to 131.3617.3 mmHg after the first treatment period with telmisartan or placebo. However, no average significant influence of telmisartan was observed compared to placebo. The latter may be due to a large interindividual variability of BP responses reaching from a 40 mmHg decrease under placebo to 40 mmHg increase under telmisartan. Antihypertensive co-medication was changed for clinical reasons in 7 out of 21 patients with no significant difference between telmisartan and placebo groups. Our starting hypothesis, that telmisartan on top of standard therapy lowers systolic office BP in HD patients could not be confirmed. In conclusion, this small trial indicates that testing antihypertensive drug efficacy in HD patients is challenging due to complicated standardization of concomitant medication and other confounding factors, e.g. volume status, salt load and neurohormonal activation, that influence BP control in HD [13]

Hemodialysis patients have uremic dyslipidemia, represented by elevated serum intermediatedensity lipoprotein cholesterol (IDL-C) levels, and an increased cardiovascular mortality rate. A study was performed to determine the low-dose effects of the angiotensin II receptor blocker losartan and the angiotensinconverting enzyme inhibitor trandolapril on pulse wave velocity (PWV), which predicts cardiovascular morbidity and mortality in hemodialysis patients. For this purposeSerum lipid levels and PWV were monitored for 12 months in 64 hemodialysis patients who were administered low doses of losartan or trandolapril or a placebo. At the start of the study, there were no differences in patient characteristics among the 3 groups. PWV tended to increase in the placebo group during the 12-month study period, but decreased signiﬁcantly in the losartan and trandolapril groups, and decreases in PWV were similar in the losartan and trandolapril groups. There were no changes in blood pressure, hematocrit, erythropoietin dose, ankle-brachial index, serum lipid levels, serum 8-isoprostane levels, or serum C-reactive protein levels during the 12-month study period, but there was an increase in serum triglyceride levels in the losartan group and a decrease in serum IDL-C levels in the losartan and trandolapril groups. In hemodialysis patients, trandolapril is as effective as losartan in decreasing PWV independent of its depressor effect and in suppressing elevated IDL-C levels. Long-term blockade of the renin-angiotensin system may have a beneﬁcial effect on the acceleration of atherosclerosis and uremic dyslipidemia [14]

A study was conducted to compare the clinical efficacy of two calcium channel blocker–based combination therapies with an angiotensin receptor blocker in Japanese patients with essential hypertension. A 16 week, double-blind, parallel-arm, randomized clinical trial was performed to compare the efficacy and safety of the combination therapy of controlled release nifedipine (nifedipine CR) plus valsartan vs. that of amlodipine plus valsartan. The primary endpoint was the target blood pressure achievement rate. Eligible patients were randomly allocated to nifedipine CR–based or amlodipine-based treatment groups. Patients were examined every 4 weeks to determine whether the blood pressure had reached the target level. When the target level was not achieved, the drug regimen was changed; when the target blood pressure was achieved, the same study medication was continued. A total of 505 patients were enrolled in the study (nifedipine CR group: 245 cases; amlodipine group: 260 cases). After 16 weeks of treatment, blood pressure was significantly reduced in both groups, but to a larger extent in the nifedipine CR group than in the amlodipine group (p<0.01). The target blood pressure achievement rate was also significantly higher in the nifedipine CR group (p <0.001). There was no significant difference in the incidence of drug-related adverse events between the groups. These results indicate that the nifedipine CR–based combination therapy was superior. To the amlodipine-based therapy for decreasing blood pressure and achieving the target blood pressure in patients with essential hypertension [15]

Rizna et al in conducted cross sectional study assessing the accuracy and relaiblity of BCM. They report that chronic ﬂuid overload and hypertension are among the leading causes of mortality in dialysis patients. The body composition monitor (Fresenius Medical Care, Bad Homburg, Germany) is a bioimpedance spectroscopy device that has been validated for the assessment of overhydration. The authors used this body composition monitor device on all patients on continuous ambulatory peritoneal dialysis centre to assess their degree of overhydration. The results included Thirty four (17 men, 17 women; mean age 44\_5 ± 14\_2 years) of a 45 continuous ambulatory peritoneal dialysis patients . The mean overhydration was 2\_4 ± 2\_4 l. Fifty per cent of the patients were \_2 l overhydrated. Overhydration correlated with male gender, low serum albumin, increasing number of antihypertensive agents and duration of dialysis. There was no difference in overhydration between diabetic and non-diabetic patients. Men were more overhydrated than women, had lower Kt/V and were older. Although, there was no difference in blood pressure between the genders, men had a trend towards a higher usage of antihypertensive agents. The study concluded that overhydration is common in peritoneal dialysis patients. Blood pressure should ideally be controlled with adherence to dry weight and low salt intake rather than adding antihypertensive agents even in the absence of clinical oedema. Body composition monitor is a simple, reliable and inexpensive tool that can be routinely used in the outpatient clinic setting or home visit to adjust the dry weight and avoid chronic ﬂuid overload in between nephrologists review

## Section II

## Research hypothesis

Since there is a constant volume variation during hemodialysis session, there is a strong possibility for the activation of RAAS system. The activation of RAAS system leads to narrowing of the lumen of blood vessels thus leading to rise in blood pressure even if the patient is euvolumic. Considering the importance of RAAS system in euvolumic hypertensive patients, the role of drugs blocking RAAS system needs further investigation. Hence the current research is based on role of ARBs in managing hypertension among euvolumic hemodialysis patients.

## Null Hypothesis

There is no difference in ARB interventional and control treatment for blood pressure control among euvolumic hypertensive dialysis patients

## Alternate hypothesis

There is difference in ARB interventional and control treatment for blood pressure control among euvolumic hypertensive dialysis patients

## Justification of study

Studies indicate that hypertension is up to 90% prevalent among haemodialysis patients. Managing hypertension among haemodialysis patients is often a difficult task. Classically, patient volume status was assessed by clinical experience. However with the advent of new technology, patient volume status is now measured with more accuracy. Body composition monitoring provides a detail and accurate picture of patient volume status.

In most clinical practice hypertensive medications to haemodialysis patients are not given on basis of their volume status since most of the clinicians don’t have an accurate idea for volume status. The use of BCM in identifying Euvolemic patients that are hypertensive provides a unique area for research. The current study will involve the role of ARB in management of hypertension among euvolumic post dialysis patients. To our knowledge, no study has assessed the role of ARB in managing hypertension among Euvolumic patients. The study will findings will have direct impact on clinical practice.

## Study objective

### Primary objective

1. To observe and compare the effect of ARBs **(Lorsartan)** in blood pressure control among Euvolemic hypertensive dialysis population.

### Secondary objective

To note the probability, severity and preventability of common occurring ADR among Euvolemic hypertensive dialysis population on ARB compared to standard

# SECTION III

# Study design

## Study type

A controlled, randomized, open label trial (parallel design)

## Methodology

The current study is a two phase study

### Phase 1 (Pre-screening Procedure)

The current study will be a two phase study carried out at chronic kidney department of Hospital Univeristi Sainsa Malaysia (HUSM). The phase one i.e is the pre-screening procedure for phase two includes prospectively assess the hydration status of hypertensive patients undergoing hemodialysis. The hydration status 30 minute post dialysis will be evaluated by Body composition monitor (BCM) that would provide reliable and accurate result for the hydration status. Blood pressure on sitting position will be recorded 15 minutes post dialysis. A detailed validated questionnaire will be designed to record patient’s clinical and demographic data. Since the purpose of phase one is to identify Euvolemic hypertensive population, once completed, Euvolemic hypertensive patient population will be informed and asked to join for randomized control trial (phase two)

### Phase II (Intervention)

Phase two involves a controlled, randomized, open label trial with add-on of ARBs involving previously identified Euvolemic hypertensive population. All patients will be provided written informed consent for the participation in the study. All enrolled patients will enter a 10 day wash out period.

Randomization will be performed by using the Covariate Adaptive Randomization method. Age, gender, year on dialysis and diabetes will be Covariate for randomization. Using this method, every time a participant was registered, the number of participants was balanced according to the stratification and simultaneously the balance of 2 groups. Concomitant antihypertensive therapy will be allowed in both groups.

## Control & Interventional group

After selection of study subjects, patients will be randomized into standard and interventional group. All efforts will be made to standardize baseline characteristics during randomization. Once randomized, the study subjects will enter the trial period. Baseline hypertensive medication in all the subjects including standardized and interventional arm will be same. On top of standard antihypertensive medication the interventional group subjects will receive ARB. The ARB used for current RCT is “Losartan”. The selection of Losartan was based on availability, cost effectiveness and expert opinion of a Nephrologist.

## Medication titration

The medication dose for each ARB will be titrated after four weeks until the target SBP of less than 140 mm Hg was achieved. If targeted blood pressure is achieved, subject will be maintained on the same dose for further four weeks and should maintain targeted blood pressure. Failure to achieve or maintain targeted blood pressure for four weeks, subjects dose will be titrated till targeted blood pressure is achieved and maintained for three weeks.

## Escalation of medication dose

### Losartan

50 mg/day for three weeks as a test dose to note any incidence of hypotension. Maximum titrated dose of 100mg/day [16].

## Duration of RCT

All patients after randomly assigned to treatment with an ARB or no ARB (control) group will be followed for 8 month.

## Data collection

Once the patients have started treatment in their respective arms, a validated data collection booklet for every patient enrolled will be given to the staff nurse. Data collection form will be validated by a group of experts, after amendments a final validated data collection form will be used. All data of patient pre, interadialytic and post dialytic will be recorded. Patient pre weight, inter dialytic weight gain, post dialytic weight gain including other information will be recorded

## Subject selection

### Eligibility criteria

Euvolumic patients with blood pressure more than 140/90 mmHg post dialysis will be included for the study. On basis of expert opinion from nephrologists, patient 30-80 years were included for current study. Finally, patients undergoing dialysis duration of at least 12 months, 2 to 3 HD sessions weekly and Patients willing to participate were inducted for current study.

### Exclusion criteria

Patients with amputations, neoplasm and cystic kidneys, unwilling to participated in the study, Patients already on ARBs and Patients with symptomatic hypotension or SBP less than 110 mm Hg were excluded from the study

## Recruitment of subjects

The study will primarily be conducted at Hospital Universiti Sains Malaysia (HUSM) and will involve multiple dialysis centers from the state of Kelantan till required sample size is achieved. These haemodialysis include dialysis centers from Pasir Tumbuh, Machang & Pasir Mas. Since all patients from dialysis centre Pasir Tumbuh, Machang and Pasir Mas are enrolled patients at HUSM and regularly visit HUSM for medical checkup hence due to ease of access, these patients provide appropriate study participants for current study. A total of 90 participants will be recruited for the study for a study period of 8 months.

## Consent for participation

A pre-planned visit to each dialysis center will be made to inform the unit management about the study. Once the dialysis unit agrees to participate for the study, a signed consent form from all the patients will be taken. All patients on sponsorship or on self financed dialysis will be given a consent form and will be thoroughly explained about the study. Appropriate time would be given to the patient for their consent to join the study. No patient will be recruited for the study unless he/she has agreed to join the study without any external or internal pressure. The consent will be taken by one of the co-authors other than nephrologists or a physician that may have any influence on decision of patient. The patient will have the right to withdraw from the study at any time. A BCM analysis 30 minute post dialysis will be conducted to evaluate patient hydration status. Upon confirmation of euvolumic hypertensive individual, the patient will be randomized and Patients will undergo a 2 week washout period to eliminate any residue from previous anti hypertensive medications. Upon completion of the washout period, patient will be given treatment according to randomized arm.

## Primary end points

The primary end point of study would be achieving targeted blood pressure of <140/90 mmHg and maintaining for three weeks

## Secondary end point

The secondary point will be all cause of mortality

### Randomization

Covariate Adaptive Randomization

### Principle

In covariate adaptive randomization, a new participant is sequentially assigned to a particular treatment group by taking into account the specific covariates and previous assignments of participants. Covariate adaptive randomization uses the method of minimization by assessing the imbalance of sample size among several covariates [17]. The Taves covariate adaptive randomization method will be used for randomization that allows for the examination of previous participant group assignments to make a case-by-case decision on group assignment for each individual who enrols in the study.

Using Covariate Adaptive Randomization patients will be assigned to treatment or control arm. Covariates considered for current study are age, gender, diabetes and year of dialysis.

## Minimizing biasness

The process used in epidemiological studies and clinical trials in which the participants, investigators and/or assessors remain ignorant concerning the treatments which participants are receiving [18]. The aim is to minimize observer bias, in which the assessor, the person making a measurement, have a prior interest or belief that one treatment is better than another, and therefore scores one better than another just because of that. In order to avoid biasness, randomization of study participants will be done by computer generated programme hence minimizing the risk of selection biasness and will devoid any influence of researcher, the prescriber or the participant on selection of group or medication. Scott et alargued that this predictability and biasness of randomization is true for all methods and it should not be overly penalized. [19]

**Washout period**

The purpose of washout period is to eliminate previously given hypertensive medication. Since all enrolled patients will be hypertensive hence care must be taken not to devoid patients too long without antihypertensive therapy. Based on pharmacokinetics of previously prescribed antihypertensive medication, all enrolled patients already on RAAS inhibitors will undergo minimum two week wash out period to avoid any biasness to study. During the washout period patients, in consultation with a cardiologist and a nephrologists, patients will be maintained on other hypertensive medication so as to maintain their blood pressure. On the completion of wash out period the patients will enter in to regular trial phase.

**Assessing Euvolumic state**

Body composition monitor is a non invasive instrument used to assess volume status, nutrition status, body composition and other important clinical aspects with precision and reliability. One of other main aspects of BCM is the measurement of dry weight for hemodilaysis patients. Attaining ideal dry weight is essential in achieving euvoluic volume status post dialysis. Hence all efforts will be done to ensure patients achieving dry weight with the use of BCM in order to achieve post dialysis euvolumic state. BCM analysis of dry weight and post dialysis euvolumic state will be done every three session to ensure patient achieving euvolumic state. Any patient once identified, unable to attain euvolumic state for more than one week or three sessions will result in drop out from the study.

**Probability, severity and intensity of ADR**

All records of common occurring ADR will be maintained throughout the study period. Probability of ADR will be conducted using naranjo scale. Whereas severity and intensity of ADR will be evaluated by Hartwig and Schumock scale respectively.

## Sample size

Sample size for current study was based on statistical superiority trial (continuous data) design of Randomized control trial. To verify that a new treatment is more effective than a standard treatment from a statistical point of view or from a clinical point of view, its corresponding null hypothesis is that: The new treatment is not more efficacious than the control treatment by a statistically/clinically relevant amount. Based on the nature of relevant amount, superiority design contains statistical superiority trials and clinical superiority trials [20].

Figure 2: equation for statistical superiority



Where,

N=size per group; p=the response rate of standard treatment group; p 0= the response rate of new drug treatment group; z = the standard normal deviate for a one or two sided x; d= the real difference between two treatment effect; a clinically acceptable margin; S= Polled standard deviation of both comparison groups

Calculating the sample size using mentioned equation

N= 2x$\left(\frac{1.96+0.845}{3}\right)$ 2 x 20.48

N= 35

The sample size calculated from statistical superiority for randomized control trial is 35 for each arm of treatment, altogether 70 euvolumic hypertensive patients will be recruited for current study. With 25% drop out rate, altogether 90 patients will be recruited for current RCT with 45 patients in each arm

## Data handling and record keeping

All BCM analysis and initial data collection will be performed by chief investigator himself. Proper patient id will be given to each patient that would be used for future reference throughout the study. Since blood pressure reading and other important clinical parameters will be noted every dialysis session, hence data collection log book will be used to note blood pressure pre, intra, post dialytic and other information. All data will be collected by the Principle investigator. Once in two month visit to HUSM of all enrolled patients will be ensured as per study protocol. During this visit patients will undergo routine examination and routine blood test (Renal profile, lipid profile, lipid profile and complete blood picture) by nephrologists and a cardiologist and will. Comments from nephrologists and cardiologist will be taken on patient log book provided by the researcher. All data collection form, incidence reporting form, patient log book will finally be kept by the principle investigator and would be used for data analysis. All data will be kept highly confidential to minimise any biasness

**Potential risk to subjects**

One of the main potential risks among the study subjects is uncontrolled hypertension. A close monitoring of patients will be ensured to minimize risks. Any patient during the trial having a systolic blood pressure >160 mmHg over three dialysis sessions will be excluded from the study. Hypotension is another risk associated with antihypertensive medication, any patient having a systolic blood pressure of <110 mmHg will also be excluded from the study. Regular blood samples will be taken to avoid any episode of ARB associated hyperkalemia and other blood abnormalities. A through record will be maintained for this purpose. Other minor side effects are common with all antihypertensive medication and include, nausea, vomiting, dizziness and headache. Participation in current study is voluntarily and all participants have a right to withdraw from the study. In case of any study related injury or the nephrologist feels that the patient might be at risk of study related injury, the patient will be withdrawn from the study immediately and treated at HUSM. Similarly in case of any ADR developed during the study, the patient will be referred to and treated at HUSM.

**Benefits for the patients**

All study subjects participating in the study will undergo a detail nephro and cardio assessment at the start, during and at the end of the trial. This detail medical check up will give a detail medical picture and would help in future direction. Potentially of finding a better antihypertensive combination for euvolumic patients would have beneficial effects for other patients elsewhere. Participating in the study patients would help in giving future directions to clinical practice in managing hypertension among haemodialysis patients.

**Statistical Analysis**

Results will be expressed as mean or percentage. Comparisons between treatment groups were made by using Student *t*-test or Mann-Whitney test when applicable for continuous variables and using test for categorical variables. Cumulative event curves will be created by means of Kaplan-Meier analysis, and differences between the 2 treatment groups were analyzed by using log-rank test.

Cox proportional hazards regression analyses were performed for comparison of the 2 treatment groups after adjustment for the dynamic stratiﬁcation variables (age, sex, years on dialysis, and diabetes) and centre effect. These data are presented as hazard ratios and 95% conﬁdence intervals. Statistical signiﬁcance was set at *P* less than 0.05. All statistical calculations will be performed using SPSS version 20.

**Declaration of conflict of interest**

All investigators have no conflict of interest to declare

# SECTION IV

## Annex A

**Patient Consent Form**

****

**EFFECT OF ANGIOTENSIN RECEPTOR BLOCKERS ON MANAGEMENT OF HYPERTENSION AMONG EUVOLEMIC HEMODIALYSIS PATIENTS: A RANDOMIZED CONTROLLED TRIAL**

 **Consent form**

**Title of study**

Effect of angiotensin receptor blockers on management of hypertension among euvolemic hemodialysis patients: a randomized controlled trial

**Purpose of study**

The purpose of the study is to evaluate the effect of Angiotensin receptor blocker in the management of euvolumic but hypertensive management patients.

**Subject consent**

I have been given the opportunity to ask questions to the researcher regarding the study. I am satisfied with the answers provided.

I confirm that I have been given enough time to think and freely take part in this research. I agree with the instructions given to me. I have received a copy of this consent form.

**Payment**

**There is no payment for participation in the study.**

**Name patient: Researcher Name:**

**ID: ID:**

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Signature patient Signature Researcher**

**Date Date**

**Witness:**

I \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ attest that the information given to the doctor was apparently understood. The subject was satisfied and informed consent was freely given by the subject.

Name:

ID:

\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Witness signature

Date

## Annex B

**Data collection Form**

**PHASE I**

**A). Demographics/ History/ Diagnosis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Patient`s Code |  | Gender | ○ Male | ○ Female |
| Age (Years) |  | Age group  | ○ >30 ○ 31-40 ○ 41-50 ○ >50 |
| Weight (kg) |  | Height (cm) |  |
| BMI |  | Resident | ○ Rural ○ Urban |
| Socio-Economic Status | ○Low (≤ RM 2300) ○ Middle (RM 2301-5600) ○ High (> RM 5600) |
| Education Level | ○ No formal Education ○ Primary ○ Secondary ○ Tertiary ○ Unclassified  |
| Diet Conditions | ○ Well Nourished ○ Malnourished |
| District | ○ Kota Bharu○PasirPuteh○ Others (Referrals)○Bachok○ Kuala Krai \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_○Pasir Mas ○Machang○Tumpat○GuaMusang○ Tanah Merah○Jeli |
| Marital Status | ○ Single ○Married ○ Widow ○ Divorced |
| Race | ○Malay ○ Chinese ○ Thai ○ Indian ○ Others: \_\_\_\_\_\_\_\_\_\_\_\_\_\_ |
| Smoking Status | ○ Ever Smoker ○ Current Smoker ○ Ex-Smoker ○ Non-Smoker |
| Alcohol | ○Current drinker ○ Ex-drinker ○ Non-drinker |
| Drug Addiction | ○ Current DA ○ Ex-DA ○ No DA |
| Employment | ○ Employed (○ Government ○ Private ○ Self Employed: \_\_\_\_\_\_\_\_\_\_\_)○ Un-employed ○ Retired ○ House Wife ○ Student |
| **DIALYSIS** |
| Number of years  | ○ 1 ○ 2-3 ○3-4 ○ 4-5 ○ >5 |  |  |
|  **CO-MORBIDITY**  |
| ○Alzheimer's disease/dementia ○Blood clots ○Cancer ○Depression○HIV○Ischemic heart disease | ○Arthritis ○Asthma ○High blood pressure ○Heart disease ○Pneumonia ○ SLE  | ○ Stroke○Pregnancy losses/birth defects ○High cholesterol ○Diabetes  ○ Hepatitis B ○ Hepatitis C  |

**PREDIALYSIS PARAMETERS**

|  |  |
| --- | --- |
| **Variables**  | **Range**  |
| Blood Pressure (mmHg) |  |
| Temperature (CO) |  |
| Pulse rate (BPM) |  |
| Shortness of breath | ○ Yes ○ No |
| Oedema  | ○ Yes ○ No |
| Effort tolerance | ○ Good ○ Moderate ○ Poor |
| **Fistula**  |  |
| Thrill Normal | ○ Yes ○ No |
| Inflammation | ○ Yes ○ No |
| Haematoma | ○ Yes ○ No |
| Heparin loading dose |  Units  |
| Pre-dialysis weight |  |
| Dry weight |  |
| Interdialytic weight gain  |  |

**INTERADIALYTIC ASSESSMENT**

|  |  |
| --- | --- |
| **VARIABLES**  | **NORMAL** |
| Blood Pressure (mmHg) |  |
| Pulse rate (BPM) |  |
| Heart rate (BPM) |  |
| Respiratory rate (BPM) |  |
| Heprin dose |  Units  |
| Blood Flow rate  |  |
| **Critical Incidence Report** |  |
| Chills | ○ Yes ○ No |
| Hypotension | ○ Yes ○ No |
| Vomiting | ○ Yes ○ No |
| Headache | ○ Yes ○ No |
| Chest pain | ○ Yes ○ No |

**POST DIALYSIS ASSESSMENT**

|  |  |
| --- | --- |
| **Variables**  | **Normal** |
| Blood Pressure (mmHg) |  |
| Temperature (CO) |  |
| Pulse rate (BPM) |  |
| Weight post dialysis |  Kgs  |
| Interdialytic weight gain  |  |
| Over hydration  |  |
| Targeted dry weight |  |
| Patient assessment  | ○ Hypervolumic Hypertensive ○ Hypovolumic Hypertensive○ Euvolumic Hypertensive○ Euvolumic Hypotensive○ Hypovolumic normotensive |
| Comfortable | ○ Yes ○ No |
| Weak | ○ Yes ○ No |
| Hypotension | ○ Yes ○ No |
| Hypertension | ○ Yes ○ No |
| Shortness of breath | ○ Yes ○ No |
| Fistula thrill (normal) | ○ Yes ○ No |
| **Critical Incidence Report** |  |
| Chills | ○ Yes ○ No |
| Hypotension | ○ Yes ○ No |
| Vomiting | ○ Yes ○ No |
| Headache | ○ Yes ○ No |
| Chest pain | ○ Yes ○ No |
| Fistula pain | ○ Yes ○ No |

**HYPERTENSIVE PHARMACOTHERAPY**

|  |  |
| --- | --- |
| Adrenergic receptor blockers | Angiotensin-receptor blockers |
| **α-Antagonist** |  | Irbesartan | ○ Yes ○ No |
| Doxazosin | ○ Yes ○ No | Losartan | ○ Yes ○ No |
| Prazosin | ○ Yes ○ No | Valsartan | ○ Yes ○ No |
| Terazosin | ○ Yes ○ No | Candesartan | ○ Yes ○ No |
| **β-Antagonist** | ○ Yes ○ No | ACE inhibitors |  |
| Abebutalol | ○ Yes ○ No | Benazepril | ○ Yes ○ No |
| Atenolol | ○ Yes ○ No | Captopril | ○ Yes ○ No |
| Bisoprolol | ○ Yes ○ No | Enalapril | ○ Yes ○ No |
| Carvedilol | ○ Yes ○ No | Fosinopril | ○ Yes ○ No |
| Labetalol | ○ Yes ○ No | Lisinopril | ○ Yes ○ No |
| Propranolol | ○ Yes ○ No | Calcium channel blockers |
| Propranolol | ○ Yes ○ No | Amlodipine | ○ Yes ○ No |
| Metoprolol | ○ Yes ○ No | Diltiazem | ○ Yes ○ No |
| Vasodilators |  | Nifedipine | ○ Yes ○ No |
| Hydralazine | ○ Yes ○ No | Nisoldipine | ○ Yes ○ No |
| Minoxidil | ○ Yes ○ No | Verapamil | ○ Yes ○ No |

|  |  |
| --- | --- |
| **Lipid Lowering Agents** |  |
| **Statins (HMG-CoA reductase inhibitors)** |  |  |  |
| Lovastatin | ○ Yes ○ No | **Cholesterol absorption inhibitors** |
| Atorvastatin | ○ Yes ○ No | Ezetimibe | ○ Yes ○ No |
| Simvastatin | ○ Yes ○ No | **Anemia Treatment** |
| Fluvastatin | ○ Yes ○ No | Oral Folic acid  | ○ Yes ○ No |
| Pravastatin | ○ Yes ○ No | Iron dextran | ○ Yes ○ No |
| Rosuvastatin | ○ Yes ○ No | Iron sucrose/Venofer | ○ Yes ○ No |
| **Fibrates (Fibric acid derivatives)** | ○ Yes ○ No | Cosmofer | ○ Yes ○ No |
| Bezafibrate | ○ Yes ○ No | **Epoietin therapy** | ○ Yes ○ No |
| Ciprofibrate | ○ Yes ○ No | Recormon | ○ Yes ○ No |
| Fenofibrate | ○ Yes ○ No | Eprex ○ Yes ○ No |
| Gemfibrozil | ○ Yes ○ No | Epocim | ○ Yes ○ No |
| **Resins (Bile-acid sequestrants)** | Epokine | ○ Yes ○ No |
| Cholestyramine | ○ Yes ○ No | Hemotin | ○ Yes ○ No |
| **Nicotinic acid** |  | GerEpo | ○ Yes ○ No |
| Acipimox | ○ Yes ○ No | Epiao | ○ Yes ○ No |
| Nicotinic acid | ○ Yes ○ No | **Calcitriol** |  |
| **Renal bone treatment**  |  | Calcitriol (Rocaltriol/one alpha) | ○ Yes ○ No |
|  |  |  |  |
| **Phosphate binders** | ○ Yes ○ No | Calcitriol (calcijex) | ○ Yes ○ No |
| CaC03 | ○ Yes ○ No | Anti-diabetic agents |  |
| Lanthanum carbonate | ○ Yes ○ No | **Sulphonyl ureas** |  |
| Aluminium binders | ○ Yes ○ No | Tolbutamide  | ○ Yes ○ No |
| SevelamerHCl | ○ Yes ○ No | Chlorpropamide  | ○ Yes ○ No |
| Anti-diabetic agents |  | Glibenglamide | ○ Yes ○ No |
| **Alpha glucosidase inhibitors** |  | Glipizide  | ○ Yes ○ No |
| Rosiglitazone  | ○ Yes ○ No | Gliclazide | ○ Yes ○ No |
| Pioglitazone  | ○ Yes ○ No | Insulin  | ○ Yes ○ No |

**LABORATORIES FINDINGS**

|  |  |
| --- | --- |
| **Renal Function Tests** | **Blood Sugars** |
| Sodium (mmol/L) | 135-145 |  |  |  | RBS (mmol/L) | 4.2-6.4 |  |  |  |
| Potassium (mmol/L) | 3-5 |  |  |  | FBS (mmol/L) | 4.1-5.5 |  |  |  |
| Urea (mmol/L) | 1.7-8.3 |  |  |  | HbA1C (%) | ≤ 7% |  |  |  |
| Creat (µmol/L) | 53-9744-80 |  |  |  |
| BUN/Cr Ratio | 5-35 |  |  |  |
| Uric acid (µmol/L) | 210-420 |  |  |  |
| Calcium (mmol/L) | 2.3-2.5 |  |  |  |
| Phosphate (mmol/L) | 0.9-1.3 |  |  |  | **Lipid Profile** |
| **Liver Function Tests** | TG (mmol/L) | 0.68-1.880.46-1.6 |  |  |  |
| TP (g/L)  | 65-83 |  |  |  | CHO (mmol/L) | ≤6.2 |  |  |  |
| Albumin (g/L) | 38-44 |  |  |  | LDL (mmol/L) | 2.33-4.52.33-4.7 |  |  |  |
| Globulin (g/L) | 23-35 |  |  |  | HDL (mmol/L) | >0.91 |  |  |  |
| AG ratio | 1.12-1.41 |  |  |  | **Complete Blood Count** |
| AST (IU/L) | 5-34 |  |  |  | WBC (×109/L) | 3.8-9.73.4-10.1 |  |  |  |
| ALP (IU/L) | 53-16842-98 |  |  |  | RBC (×1012/L) | 4.2-6.1053.52-5.16 |  |  |  |
| ALT (IU/L) | 10-35 |  |  |  | PLT (×109/L) | 158-410 |  |  |  |
| TBR (µmol/L) | <17 |  |  |  | HGB (g/dL) | 12-16.59.81-13.85 |  |  |  |
| DBR (µmol/L) | <4.3 |  |  |  | HCT (%) | 37.5-49.831.8-42.4 |  |  |  |
|  |  |  |  |  | Amylase (U/L) | 25-125 |  |  |  |

## Annex C

**Patient Booklet**

**Phase II**

|  |  |  |  |
| --- | --- | --- | --- |
| Patient`s Code |  | Date  |  |
| Time arrival |  | Staff name (starting)  |  |
| Time left |  | Staff name (ending) |  |
| Time start |  | Time end |  |
| Treatment start date |  | Dialysis centre |  |
|  |  |
| Session number  |  |
| Treatment type | ○ Standard ○ Intervention  |
| Dry weight (bcm) |  |
| Medication  | 1. \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_dose\_\_\_\_\_\_\_\_\_\_\_\_
2. \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_dose\_\_\_\_\_\_\_\_\_\_\_\_
3. \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_dose\_\_\_\_\_\_\_\_\_\_\_\_
4. \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_dose\_\_\_\_\_\_\_\_\_\_\_\_
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**PREDIALYSIS PARAMETERS**

|  |  |
| --- | --- |
| **Variables**  | **Range**  |
| Blood Pressure (mmHg) |  |
| Pulse rate (BPM) |  |
| Shortness of breath | ○ Yes ○ No |
| Oedema  | ○ Yes ○ No |
| Effort tolerance | ○ Good ○ Moderate ○ Poor |
| **Fistula**  |  |
| Thrill Normal | ○ Yes ○ No |
| Inflammation | ○ Yes ○ No |
| Haematoma | ○ Yes ○ No |
| Heparin loading dose |  Units  |
| Pre-dialysis weight |  |
| Interdialytic weight gain  |  |

**INTERADIALYTIC ASSESSMENT**

|  |  |
| --- | --- |
| **VARIABLES**  | **NORMAL** |
| Blood Pressure (mmHg) |  |
| Pulse rate (BPM) |  |
| Heprin dose |  Units  |
| **Critical Incidence Report** |  |
| Chills | ○ Yes ○ No |
| Hypotension | ○ Yes ○ No |
| Vomiting | ○ Yes ○ No |
| Headache | ○ Yes ○ No |
| Chest pain | ○ Yes ○ No |
| Leg cramps  | ○ Yes ○ No |

**POST DIALYSIS ASSESSMENT**

|  |  |
| --- | --- |
| **Variables**  | **Normal** |
| Blood Pressure (mmHg) |  |
| Pulse rate (BPM) |  |
| Weight post dialysis |  Kgs  |
| **Post dialysis patient assessment**  |  |
| Comfortable | ○ Yes ○ No |
| Weak | ○ Yes ○ No |
| Hypotension | ○ Yes ○ No |
| Hypertension | ○ Yes ○ No |
| Shortness of breath | ○ Yes ○ No |
| Fistula thrill (normal) | ○ Yes ○ No |
| **Critical Incidence Report post dialysis**  |  |
| Chills | ○ Yes ○ No |
| Hypotension | ○ Yes ○ No |
| Vomiting | ○ Yes ○ No |
| Headache | ○ Yes ○ No |
| Chest pain | ○ Yes ○ No |
| Fistula pain | ○ Yes ○ No |
| Leg cramps  | ○ Yes ○ No |

|  |  |
| --- | --- |
| **General remarks**  | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |

**Endorsement from head nurse**

|  |  |
| --- | --- |
| **Name**  |  |
| **Signature**  |  |
| **Date**  |  |

## Annex D

**Doctor note book**

**Nephrologist notes**

|  |  |
| --- | --- |
| **Date**  | **Comments**  |
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**Cardiologist comments**

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| **Date**  | **Comments**  |
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## Annex E

## Gantt Chart

|  |  |  |  |
| --- | --- | --- | --- |
|  | 1st year | 2nd year | 3rd year |
| **Literature review** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Ethical & MOH approval** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Data collection** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Publication** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Conference** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Thesis writing** |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |

**Flow chart**

Dialysis patients

BCM analysis

Post dialysis Hypervolumic

Post dialysis Euvolumic

Post dialysis Hypovolumic

Euvolumic Hypertensive

>140/90 mmHg

N=90

Euvolumic Normotensive

<140/90 mmHg

Randomization (n=90)

Covariate adaptive randomization

Standard Arm

N= 45

Interventional Arm

N=45

Wash out period

Wash out period

Cardiovascular assessment

Cardiovascular assessment

Treatment

Treatment

Trial completion

Trial completion

Cardiovascular assessment

Cardiovascular assessment

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