THESIS PROTOCOL

TITLE

EFFECTS OF DOXERCALCIFEROL COMPARED TO CALCITRIOL FOR LOWERING PARATHYROID HORMONE LEVEL IN PATIENTS ON HEMODIALYSIS

NCT Number -Not Yet

Date-13 May 26

INVESTIGATOR:

DR. A.K.M. Arshadul Abbas

Resident

MD (Nephrology) Phase-B

Session: March, 2024

GUIDE:

Prof. Dr. MdNurul Huda

MBBS, MCPS (Medicine),FCPS (Medicine),

MD (Nephrology),FASN

Professor and Head

Department of Nephrology

Chittagong Medical College and Hospital

CO-GUIDE:

Dr. Md. FaizurRahman

MBBS, MCPS, MD **(**Nephrology),

Assistant Professor

Department of Nephrology

Chittagong Medical College and Hospital

To

The Principal
Chittagong Medical College
Chattogram.

Subject: Application for the approval of Thesis Protocol with the title, "**Effects of Doxercalciferol Compared to CalcitriolFor Lowering Parathyroid Hormone Level in Patients on Hemodialysis"**

Sir,

With due respect and humble submission, I would like to state that I am a student of MD Phase-B (Nephrology), at BSMMU, Dhaka. As per requirement of the course, I would like to perform my research work on the thesis with the above-mentioned title under the direct supervision of Prof. Dr. Md. Nurul Huda, Professor and Head, Department of Nephrology, Chittagong Medical College and Hospital, Chattogram, Bangladesh.

I therefore, like to request you to approve my protocol so that I can commence my work in your esteemed institute to complete my thesis in due time.

Obediently Yours

DR. A.K.M. Arshadul Abbas
MD (Nephrology-Phase B)
Department of Nephrology
Chittagong Medical College and Hospital
Chattogram, Bangladesh

CMC Ethical Review Committee

Chattogram Medical College
Chattogram-4000, Bangladesh
Tel-031619400, Fax-630180

Application for Ethical Clearance of Studies for post-Graduate Thesis

1.	Name of the applicant	:	**DR. A.K.M. Arshadul Abbas**
2.	Course	:	MD (Nephrology-Phase B)
3.	Category	:	Private
4.	Title of the study	:	Effects of Doxercalciferol Compared to Calcitriol For Lowering Parathyroid Hormone Level in Patients on Hemodialysis
5.	Type of the study	:	Randomized controlled trail
6.	Duration of the study	:	One year and six month
7.	Any collaboration	:	No
8.	Conflict of interest	:	None
9.	Name of the Guide	:	Prof. Dr. MdNurul Huda Professor and Head, Department of Nephrology, Chittagong Medical College and Hospital, Chattogram, Bangladesh
10.	Name of the Co-Guide	:	Dr. Md. FaizurRahman MBBS,MCPS MD (Nephrology) Assistant Professor, Department of Nephrology, Chittagong Medical College and Hospital, Chattogram, Bangladesh

Check Documents being submitted herewith to committee:

1.	Summary	**:** Attached
2.	Umbrella proposal initially	**:** NA
3.	Protocol and CRF	**:** Attached
4.	Informed consent form for subject	**:** Attached
5.	Verbal consent form for subjects	**:** NA
6.	Procedure for Maintaining Confidentiality	**:** Attached
7.	Schedule of the study	**:** Attached

Declaration

I agree to obtain approval of the Ethical Review Committee for any changes involving the rights and welfare of subjects or any changes of the methodology before making any such changes.

……
Principal investigator/Student

DR. A.K.M. Arshadul Abbas
MD (Nephrology-Phase B)
Department of Nephrology
Chittagong Medical College and Hospital
Chattogram, Bangladesh

Forwarding from the Guide

……
Guide

Prof. Dr. MdNurul Huda,
Professor and Head,
Department of Nephrology,
Chittagong Medical College and Hospital,
Chattogram, Bangladesh

CHITTAGONGMEDICAL COLLEGE

Application for the Ethical review of thesis protocol

1.	Name of the applicant	:	DR. A.K.M. Arshadul Abbas
2.	Course	:	MD (Nephrology Phase B)
3.	Category	:	Private
4.	Title of the study	:	Effects of Doxercalciferol Compared to Calcitriol For Lowering Parathyroid Hormone Level in Patients on Hemodialysis
5.	Type of the study	:	Randomized controlled trail
6.	Duration of the study	:	One year and six month
7.	Any collaboration	:	No
8.	Conflict of interest	:	None
9.	Name of the Guide	:	Prof. Dr. MdNurul Huda Professor and Head, Department of Nephrology, Chittagong Medical College and Hospital, Chattogram, Bangladesh
10.	Name of the Co-Guide	:	Dr. Md. FaizurRahman MBBS,MCPS MD (Nephrology) Assistant Professor, Department of Nephrology, Chittagong Medical College and Hospital, Chattogram, Bangladesh
11.	Signature of the Guide	:	
12.	Signature of the Co-Guide	:	
13.	Submission date	:	
14.	Signature of the Student	:	

For Official use:		
Serial No:	Received on:	Reviewed on:
Comment:		

Member-Secretary ERB Chairperson ERB

Circle the appropriate answer to each of the following

(If not Applicable write NA)

1. Source Population:			**4. Are subjects clearly informed about:**		
(a) Ill Subjects	√Yes	No	(a) Nature and purpose of the study	√Yes	No
(b) Non* ill subjects	Yes	√No	(b) Procedures to be followed including alternatives used	√Yes	No
(c) Minors or persons under guardianship	Yes	√No	(c) Physical risks	√Yes	No
			(d) Private questions	√Yes	No
2. Does the study involve:			(e) Invasion of the Body	√Yes	No
(a) Physical risks to subjects	√Yes	No	(f) Benefits to be Derived	√Yes	No
(b) Social risks	Yes	√No	(g) Right to refuse to participate or withdraw from the study	√Yes	No
(c) Psychological risks to subjects	Yes	√No	(h) Confidential handling of data	√Yes	No
(d) Discomfort to Subjects	√Yes	No	(i) Compensation where there are risks or loss of working time or privacy is involved in any particular procedure	√Yes	No
(e) Invasion of the body	√Yes	No			
(f) Invasion of privacy	Yes	√No			
(g) Disclosure of information damaging to subject or others	Yes	√No	5. Will informed consent be required		
			(a) From subject	√Yes	No
			(b) From parent or Guardians	Yes	√No
3. Does the study involve:					
(a) Use of records (hospital, medical, death, birth or other)	Yes	√No	**6. Will precautions will be taken to protect anonymity of subjects**	√Yes	No
(b) Use of fetal tissue or abortus	Yes	√No			
(c) Use of organs or body fluids	Yes	√No			

Chittagong Medical College
Chattogram-4000, Bangladesh
Tel-031619400, Fax-630180

Research Proposal

For Post Graduate Thesis/Dissertation

Part - A

1.	Title of the study	:	Effects of Doxercalciferol Compared to Calcitriol For Lowering Parathyroid Hormone Level in Patients on Hemodialysis
2.	Name of the applicant	:	DR. A.K.M. Arshadul Abbas
3.	Course	:	MD (Nephrology Phase B)
4.	Place of Study	:	Department of Nephrology, Chittagong Medical College Hospital, Chattogram.
5.	Sponsoring	:	Not Applicable
6.	Duration of the study	:	Eighteen month.
7.	Date of Commencement	:	
8.	Date of completion	:	
9.	Total cost	:	6,40,000/=

10. Other support of proposed research
    - i. : In this research project being supported by any other source? No
    - ii. Has an application for funding of this project has been submitted to any other organization (s)? No
11. Date of submission :
12. Signature of student :
13. Signature of Guide :
14. Endorsement of the course coordinator
    - Name and Signature
    - Designation
    - Official Seal

Part – B

Student's Information Sheet

1.	Name	:	DR. A.K.M. Arshadul Abbas
	Designation	:	Student, MD (Nephrology Phase B)
	Official address with telephone & mail	:	Department of Nephrology, Chittagong Medical College Hospital, Chattogram Phone: 01712985290 Email: arshadulabbas@gmail.com
	Present residential address	:	Khalifa Para, 4 No. ward, Chandgaon, Chottogram.
2.	Academic Background	:	

Degree	Institute	University/Board	Field	Year
M.B.B.S	Tairunnessa Memorial Medical College & Hospital	Dhaka	Passed	2010

3.	Field of study	:	Nephrology
4.	Research experience	:	None
5.	Percentage of time to be devoted to this project	:	100%
6.	Number of Scientific Publication	:	None

……..

Signature of the Student

PART-C

Title: Effects of Doxercalciferol Compared to CalcitriolFor Lowering Parathyroid Hormone Level in Patients on Hemodialysis

Summary

Background: Secondary hyperparathyroidism (SHPT) in advanced CKD results from phosphate retention and vitamin D deficiency, leading to elevated PTH levels that increase bone and cardiovascular risks. Active vitamin D analogs such as calcitriol and doxercalciferol help manage SHPT by suppressing PTH, although they differ in pharmacokinetics and effects on mineral metabolism. Intravenous formulations may provide better bioavailability and adherence than oral options, particularly in dialysis patients with absorption challenges.**Aims:** The study aims to compare the effectiveness of intravenous doxercalciferol and oral calcitriol in reducing parathyroid hormone (PTH) levels in patients undergoing hemodialysis. **Materials and Methods:** A Randomized control trailwill be conducted in the Department of Nephrology of Chittagong Medical College Hospital including 98 adult hemodialysis patients with secondary hyperparathyroidism. Participants will receive either intravenous Doxercalciferolor oral Calcitriol. **Statistical analysis:** Continuous variables will be presented as mean ± standard deviation, and categorical variables as frequencies and percentages. Independent t-tests will be used to compare means between groups, while chi-square or Fisher's exact tests will analyze categorical outcomes. The primary analysis will be an intention to treat or per protocol which one is applicable and will be analysis performed with SPSS-27.0. A p-value of less than 0.05 will be considered statistically significant for all analyses. Distributions will be expressed by mean and standard deviation for continuous variables and by frequency and percentage for qualitative variables.**Conclusion:**If intravenous doxercalciferol demonstrates improved effectiveness and a better safety profile, it could help physicians manage secondary hyperparathyroidism in hemodialysis patients more efficiently.

PART-D

1. Introduction:

Secondary hyperparathyroidism (SHPT), characterized by severely elevated parathyroid hormone levels (PTH), arises from the metabolic abnormalities of end-stage renal disease (ESRD), affecting the majority of patients undergoing dialysis and contributing to risks such as cognitive decline due to PTH's ability to cross the blood–brain barrier and affect brain function (Mathur et al. 2022). SHPT begins early in chronic kidney disease (CKD), typically during stage G2, when impaired phosphate excretion stimulates parathyroid cells to secrete more PTH, even before serum phosphate levels become elevated (Rodzon-Norwicz et al. 2023). As CKD progresses, particularly in stages G4 and G5, hyperphosphatemia and hypocalcemia become more prominent, further stimulating PTH secretion and creating a pathological cycle of glandular hypertrophy and hormonal excess (Habaset al. 2021). Clinically, SHPT leads to chronic kidney disease–mineral and bone disorder (CKD-MBD), marked by bone pain, spontaneous fractures, soft tissue calcification, and muscle weakness (Shah et al. 2024). It also contributes to serious cardiovascular complications, including vascular calcification and hypertrophic cardiomyopathy, which are major contributors to morbidity and mortality in dialysis patients (Galassi et al. 2021; (Rodzon-Norwicz et al. 2023). Without appropriate intervention, these effects significantly reduce quality of life and survival in CKD patients.

Parathyroid hormone (PTH), the main regulator of calcium balance, maintains calcium levels by mobilizing both calcium and inorganic phosphate from bone through osteoclast activation. Though it increases phosphate levels, PTH simultaneously reduces phosphate reabsorption in the renal tubules, increasing phosphaturia to compensate(Rodzon-Norwicz et al 2023). Chronic elevation of PTH in secondary hyperparathyroidism (SHPT) leads to mineral and bone disorders, such as renal osteodystrophy and vascular calcifications, which heighten cardiovascular risk(Stack, 2024). High-turnover bone disease, characterized by increased osteolysis and fibrosis, results from persistently elevated PTH levels (often >800 pg/mL), severely affecting bone integrity(Muppidiet al 2020). CKD-related imbalances in calcium and phosphate further exacerbate chronic kidney disease-mineral bone

disorder (CKD-MBD), which includes pain, fractures, soft tissue calcifications, and increased mortality due to cardiovascular events(Shah et al. 2024; Salera et al. 2025). Additionally, higher iPTH levels correlate with increased uric acid and systemic inflammation in patients with cardiovascular disease (CVD), reinforcing the systemic impact of PTH dysregulation (Checa-Roset al. 2025).

Intravenous doxercalciferol and oral calcitriol are both active vitamin D analogs used to manage secondary hyperparathyroidism (SHPT) in hemodialysis patients, but they differ in pharmacologic properties and clinical application. Oral calcitriol, the active form of vitamin D, binds directly to vitamin D receptors, effectively lowering parathyroid hormone (PTH) levels but often at the cost of increased serum calcium and phosphate levels, leading to higher vascular calcification risk (Thadhani et al., 2020). In contrast, doxercalciferol, a synthetic vitamin D analog, is a prodrug requiring hepatic activation. When administered intravenously, it produces a more stable PTH suppression with fewer calcemic side effects (Yang et al., 2025). A recent randomized trial found that doxercalciferol suppressed PTH by over 40% in 72.5% of patients compared to 58% in the calcitriol group (Yang et al., 2025), with SHPT prevalence reaching 86% in dialysis cohorts (Thadhani et al., 2020). Clinical preference now favors intravenous doxercalciferol in dialysis due to its dosing control and reduced hypercalcemia risk.

Recent clinical trials and meta-analyses have provided comparative insights into the effectiveness of calcitriol and doxercalciferol in managing secondary hyperparathyroidism in hemodialysis patients. A multicenter phase II trial revealed that intravenous doxercalciferol suppressed parathyroid hormone (PTH) levels by over 40% in 72.5% of patients, compared to 58% for oral calcitriol (Yang et al., 2025). Moreover, a recent meta-analysis indicated that doxercalciferol was associated with a significantly lower risk of hypercalcemia compared to calcitriol (Abreu et al., 2021). In practical terms, the prevalence of secondary hyperparathyroidism in hemodialysis patients is approximately 86% (Thadhani et al., 2020). Additionally, evidence suggests that calcitriol effectively reduces PTH but leads to higher serum calcium and phosphate levels, increasing vascular calcification risks, while

doxercalciferol maintains better biochemical balance with fewer adverse events (Magagnoli et al., 2024). These findings emphasize a clinical shift favoring intravenous doxercalciferol for safer and more stable management of PTH levels in this high-risk population.

In countries like Bangladesh and other low-to-middle income regions, the growing burden of chronic kidney disease and dependence on maintenance hemodialysis pose substantial public health challenges. The cost and accessibility of medications become critical factors influencing treatment decisions. While oral calcitriol is widely available and inexpensive, intravenous options like doxercalciferol may be limited to tertiary hospitals or urban dialysis units. Additionally, patient adherence to oral therapy can be inconsistent due to pill burden, gastrointestinal disturbances, and lack of awareness. In such settings, evidence that supports the use of one agent over the other, especially if it demonstrates better biochemical control or fewer side effects, is of immense value. Therefore, evaluating the comparative efficacy and safety of these two agents within a regional context is not only timely but essential for developing cost-effective, practical, and evidence-based SHPT treatment protocols for dialysis patients in resource-constrained environments.

Despite the widespread use of calcitriol and doxercalciferol in dialysis centers, the literature still lacks high-quality, head-to-head comparisons focusing specifically on hemodialysis patients in low-resource environments. Most existing data derive from Western populations, and generalizability to LMICs remains uncertain. Moreover, the impacts of administration routes on patient compliance, PTH suppression, and adverse event profiles are yet to be fully elucidated. Given the rising incidence of CKD in South Asia, a comparative evaluation of intravenous doxercalciferol and oral calcitriol in terms of PTH control, safety outcomes, and patient practicality is highly relevant. This study aims to fill this critical evidence gap and inform clinical decision-making tailored to the realities of resource-constrained settings.

2. Rationale

The route of administration plays a crucial role in determining treatment outcomes in patients with secondary hyperparathyroidism (SHPT) undergoing hemodialysis. Oral calcitriol can be hard to manage due to poor adherence from the high pill burden. In contrast, IV administration of doxercalciferol after hemodialysis provides a practical and patient-friendly alternative, as it eliminates the need for extra cannulation by utilizing the existing vascular access used during dialysis.While previous studies have reported that IV doxercalciferol achieves better outcomes in lowering parathyroid hormone (PTH) levels compared to oral calcitriol, it remains unclear whether these benefits are reproducible in our local patient population. Given the rising prevalence of SHPT and the expansion of hemodialysis services in Bangladesh, it is essential to investigate whether IV doxercalciferol can provide clinical benefits in this setting. Therefore, this study aims to evaluate the comparative effectiveness of IV doxercalciferol versus oral calcitriol in controlling PTH levels among hemodialysis patients, addressing a critical gap in local clinical evidence to inform optimal treatment strategies.

3. Research question/Hypothesis:

3.1 Research question: What is the effect of intravenous doxercalciferol compared to oral calcitriol in reducing parathyroid hormone (PTH) levels among patients undergoing hemodialysis?

3.2 Research hypothesis: Intravenous doxercalciferol ismore effective than oral calcitriol in reducing parathyroid hormone (PTH) levels in patients undergoing hemodialysis.

4. Objectives

4.1 General objectives: To compare the effectiveness and safety of intravenous doxercalciferol and oral calcitriol in reducing parathyroid hormone (PTH) levels in patients undergoing hemodialysis.

Specific objectives:

1. To detect and compare the reduction of serum parathyroid hormone (PTH) levels following treatment with intravenous doxercalciferol and oral calcitriol in hemodialysis patients.
2. To assess the changes in serum calcium and phosphate levels associated with each treatment modality.
3. Toevaluate the incidence of treatment-related hypercalcemia and hyperphosphatemia in both treatment groups.
4. To compare the adverse events and efficacy profiles of intravenous doxercalciferol and oral calcitriol in the management of secondary hyperparathyroidism in hemodialysis patients.

5. Materials and method:

5.1. Type of study: Randomized controlled trial

5.2 Place of Study: Department of Nephrology, Chittagong Medical College Hospital, Chattogram, Bangladesh.

5.3 Study period: One and half year from acceptance of protocol.

5.4 Study population: The study population will include adult hemodialysis patients with secondary hyperparathyroidism attending in the Nephrology department, CMCH will be the study population during the study period.

5.5 Sampling technique: Consecutive sampling. From the Selected participants, the intervention and control will be randomly assigned in a 1:1 ratio (block size of four) through computer- generated randomization.

5.6Inclusion criteria:

1. Adult patients aged 18 years or older.
2. Diagnosed with secondary hyperparathyroidism (SHPT) with elevated serum PTH levels (>300 pg/mL).
3. Undergoing maintenance hemodialysis for at least 3 months.
4. Patients on calcitriol therapy after washout period of 40 hrs.

5.7 Exclusion criteria:

1. Patients with known case of primary hyperparathyroidism or parathyroidectomy.
2. Serum calcium>10mg/dL or phosphate>5.5mg/dL at baseline.
3. Active liver disease or significant hepatic dysfunction, Alcoholism.
4. History of hypersensitivity to vitamin D analogs.
5. Pregnant or breastfeeding women.
6. Concurrent use of medications (e.g. bisphosphonates).
7. Patients with active malignancy.(e.g. multiple myeloma,bronchogenic carcinoma).

5.8. Sample size:

To calculate sample size for case control, study the comparison between two means, the following formula was followed (Hoque, 2014)

$$n = \frac{(Z_a + Z_b)^2 \times (s_1^2 + s_2^2)}{(m_1 - m_2)^2}$$

Here,

m_1 = 342.0 (mean of iPTH in oral cholicalciferol group)

m_2 = 279.0 (mean of iPTH in intravenous doxercalciferol group)

s_1 = 42.0 (Standard deviation of oral cholicalciferol group)

s_2 = 90.0 (Standard deviation of intravenous doxercalciferol group)

Z_a = Z value (two tail) of standard normal distribution at 95% confidence level or 5% level of significance = 1.96 (when α = 0.05 at 5% level of significance)

Z_b = Z value at 90% power = 1.28 (when β = 0.1 and Power = 1-β)

Therefore,

$$n = \frac{(1.96 + 0.85)^2 \times \{(42.0)^2 + (90.0)^2\}}{(342.0 - 279.0)^2}$$

$$= 42.8$$

This study is a follow-up study, necessitating a 15% increase in the sample size to compensate for dropout cases during the follow-up period. Consequently, the total sample size amounted to 49 cases, comprising 43 estimated sample size plus an additional 6.

Therefore, total sample size was 98 (49×2).

All values were taken from Aggarwal et al. (2011).

5.9 List of Variables

Variables	Type	Value	Expression
Sociodemographic Variables			
Age	Discrete	In completed years	Mean ± SD
Sex	Categorical	Male / Female	Frequency (%)
Monthly income	Continuous	In local currency (BDT/USD)	Mean ± SD / Median (IQR)
Height	Continuous	In centimeters (cm)	Mean ± SD
Weight	Continuous	In kilograms (kg)	Mean ± SD
BMI	Continuous	In kg/m²	Mean ± SD
Clinical Variables			
Diabetes Mellitus (DM)	Categorical	Present / Absent	Frequency (%)
Hypertension (HTN)	Categorical	Present / Absent	Frequency (%)
Blood pressure	Continuous	In mmHg	Mean ± SD
Duration of Hemodialysis	Continuous	In months or years	Mean ± SD
Biochemical Variables			
Serum Calcium (S. Ca)	Continuous	In mg/dL	Mean ± SD
Serum Phosphate (Po4)	Continuous	In mg/dL	Mean ± SD
Parathyroid Hormone (PTH)	Continuous	In pg/mL	Mean ± SD

Operational definitions:

Parathyroid Hormone (PTH): Parathyroid Hormone (PTH) will be measured as intact PTH (iPTH) in picograms per milliliter (pg/mL) using a second-generation immunoassay. In accordance with KDIGO recommendations, for patients receiving maintenance hemodialysis, iPTH levels sustained above 300 pg/mL are considered indicative of secondary hyperparathyroidism (SHPT).

Doxercalciferol: Doxercalciferol will be administered intravenously post-hemodialysis in doses ranging from 1–4 micrograms per session. Its use will follow KDIGO recommendations for selective vitamin D receptor activator (VDRA) therapy to suppress iPTH levels while minimizing the risk of hypercalcemia and hyperphosphatemia in dialysis patients.

Calcitriol: Calcitriol will be administered orally on a daily or alternate-day schedule, titrated based on iPTH, calcium, and phosphate levels.

Maintenance Hemodialysis: Maintenance hemodialysis is defined as a twice-weekly dialysis regimen maintained for a minimum duration of three months in patients with end-stage kidney disease, consistent with KDIGO standards for long-term renal replacement therapy.

Secondary Hyperparathyroidism (SHPT): Secondary hyperparathyroidism (SHPT) is defined as a chronic elevation of iPTH above 300 pg/mL in patients undergoing maintenance hemodialysis, with supporting evidence of disrupted calcium, phosphate, and vitamin D metabolism as outlined in KDIGO guidelines for CKD-MBD.

Adverse Events: An AE is defined as any untoward medical occurrence in a clinical trial patient during the study, the event does not necessarily have a causal relationship with that treatment. Therefore, an AE can be any unfavorable and unintended sign (including any clinically significant abnormal laboratory finding), symptoms, or disease, temporally associated with using a medicinal product.

Major adverse events: Will defined as any event leading to admission or prolonged admission, anaphylactic reactions, withdrawal, or death.

Minor adverse events: Will defined as minor if it does not require admission to the hospital or withdrawal of the drug. Such as nausea, vomiting, edema, headache, fatigue, metallic test, loss of appetite, constipation.

Withdrawal criteria:

- Drug intolerance or patient refusal to continue medication due to adverse effects like nausea, anorexia, vomiting, etc.
- The patient wanted to withdraw himself from the study.
- If any participant became pregnant during the study period.

5.10 Data collection instrument: A structured pretested case record form.

5.11 Data collection procedure:

All ESRD patients on hemodialysis will be consecutively and prospectively screened according to the above inclusion and exclusion criteria to identify eligible participants for randomization.Eligible patients and their legal relatives will then fully explain the study protocol, their role in the study, and the risks of the study. They will be informed of their right to withdraw from the study at any stage. After getting written informed consent, they will be finally enrolled in the study.

- **Baseline evaluation:**Baseline data will be collected at enrollment, including demographic and anthropometric variables such as age, sex, monthly income, height, weight, and body mass index (BMI). These variables will be recorded systematically for both groups to ensure proper group characterization and comparability.In addition, clinical information will be documented, focusing on the presence of comorbidities such as diabetes mellitus (DM) and hypertension (HTN). Baseline serum calcium, serumphosphate, iPTH will be recorded in the case record form. washout period of calcitriol will be conducted prior to randomization.
- **Randomization:** After consenting, eligible individuals will be recruited consecutively and randomly assigned in 1:1 ratio (block size of four), with a computer-generated randomization list, to one of the two treatment arms (Experimental group and Control group). Group 1 (Control Group) Will received oral calcitriol alone with standard treatment of CKD. Group 2 (Experimental Group) will received post-hemodialysis intravenous (IV) doxercalciferol alone with standard treatment of CKD. All participants, regardless of group allocation, who are on calcium acetate or sevelamer will continue these medications at their existing doses throughout the study period.
- **Blinding:** Blinding of the study medication is not possible because of resource limitations. It is an open-label study and both the researcher and the subject know about the drugs they are receiving.

Sample Collection procedure: Blood samples will be collected pre-dialysis after an overnight fasting period, with all aseptic precaution 5 mL of venous blood drawn into appropriate vacutainers.

- iPTH will be measured using a chemiluminescence immunoassay (CLIA).
- Serum calcium and phosphate will be analyzed using colorimetric methods on a Beckman Coulter AU480 or equivalent validated clinical chemistry analyzer.

All laboratory analyses will be conducted in an ISO-certified laboratory, ensuring accuracy and standardization of results.

Treatment: The treatment phase will last for twelve weeks. Experimental subjects will receive an intravenous loading dose of doxercalciferol 4 micrograms after dialysis, in addition to their standard routine medications. Each Dose of doxercalciferol will be given after skin sensitivity test. Skin sensitivity test will be performed by a small amount of doxercalciferol inject intradermaly→ wait 10-15 minutes → see for localized swelling and redness. Though skin sensitivity test negative despite patients may developed anaphylactic reaction, Then following measure will be taken. Prevent further contact with allergen, ensure airway patency, anti histamine, hydrocortisone, nebulize with sulbutamol, adreline, i/v fluids. Patients in the control group will receive oral calcitriol 0.25 micrograms once daily, along with their standard routine medications**.**

Evaluation of the patient at 6 Weeks: The patients will be followed up at 6 weeks (±2 days) and will instructed to report immediately in case of any advance events following consumption of the drug. Tolerability will be assessed using an adverse event profile (adverse events, serious adverse events). Safety population consist of subjects who receive at least one dose of study medication. Body weight and sitting blood pressure will be evaluated. patients will be removed if any of the withdrawals mentioned above are observed, and appropriate management will be initiated in the nephrology department of CMCH.

Follow –up and outcome assessment: All the patients will be examined again after 12 weeks (±2 days) The same biochemical parameters—serum calcium, serum phosphate, iPTH,—will be reassessed under the same collection and analysis protocols. These follow-up results will be compared with baseline values to evaluate the relative efficacy of IV doxercalciferol versus oral calcitriol in controlling SHPT and maintaining mineral balance. All data, including demographic, clinical, and laboratory results, will be systematically documented in a Case Record Form (CRF) to ensure completeness and integrity of the dataset.

- If a patient does not return for a scheduled visit, every effort will be made to contact the patient. If possible, every effort will be made to document patient outcomes in any circumstance. The Investigator will enquire about the reason for withdrawal, request that the patient return all unused study medication, ask that the patient return for a fmal visit, if applicable, and follow up with the patient regarding any unresolved adverse events.

5.12. Data analysis:

Statistical analysis will be performed using Statistical Package for Social Science (SPSS) version 27.0 (IBM Corp., Armonk, NY, USA). Baseline continuous variables such as age, monthly income, height, weight, BMI, blood pressure, duration of hemodialysis, and biochemical markers (serum calcium, phosphate, parathyroid hormone, and serum creatinine) will be expressed as mean ± standard deviation (SD) or median with interquartile range (IQR) depending on data distribution, while categorical variables such as sex, presence of diabetes mellitus (DM), hypertension (HTN) use will be presented as frequencies and percentages. Normality of continuous variables will be assessed using the Shapiro-Wilk test. For comparison between the control and experimental groups, independent samples t-test or Mann-Whitney U test will be applied for continuous variables, depending on their distribution, and Chi-square test or Fisher's exact test will be used for categorical variables. Biochemical parameters (serum calcium, phosphate, PTH, and serum creatinine) at baseline and after 12 weeks of follow-up will be compared within each group using paired t-test or Wilcoxon signed-rank test as appropriate. A p-value of less than 0.05 will be considered statistically significant.

5.13. The utilization of results:

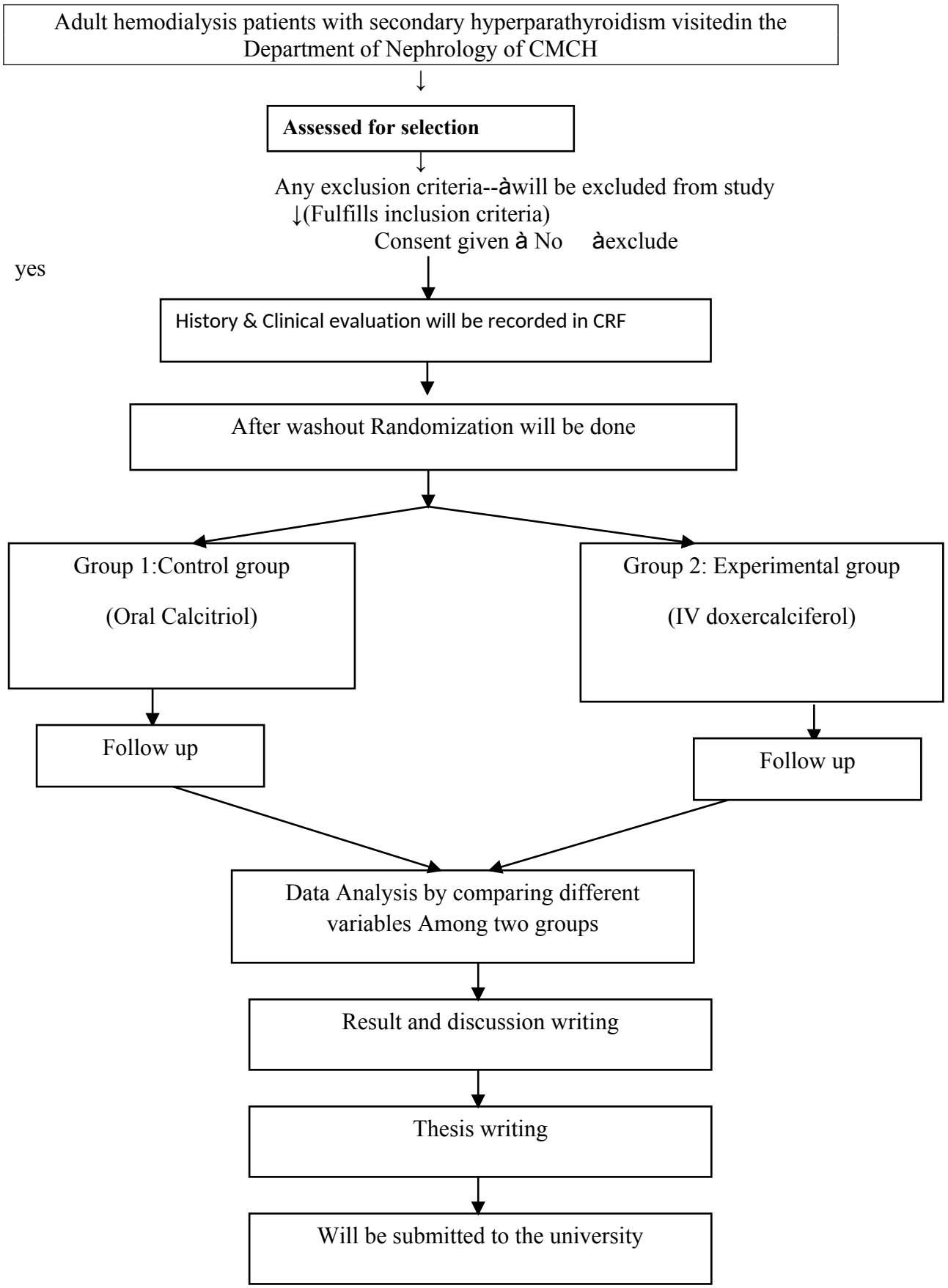
- The results will guide clinicians in selecting the optimal therapy for managing secondary hyperparathyroidism in hemodialysis patients, potentially favoring intravenous doxercalciferol over oral calcitriol, thereby improving patient outcomes and therapeutic strategies in nephrology practice.
- Efforts will also be made to present these results at conferences and publish them in peer-reviewed national and international journals.
- The results and observations of the study will be published as a thesis and submitted to the respective University as a part of the requirement for the MD (Nephrology) Phase-B examination purpose.
- The results of the study will be presented to the Department of Nephrology, CMCH.

5.14. Ethical Implication: The study will be conducted after the approval of the Ethical Review Committee of Chittagong Medical College. Voluntary written consent will be taken from the patient and legal guardians. All measures will be taken to protect anonymity. To do so, the name and address of the patient will be recorded on a separate sheet and specific codes will be put to the examination schedule and used for data collection. The interviews of the patient, clinical examination and investigations will be performed at the respective hospital after explaining the nature and purpose of the study to them, assuring that the information given by them will be used for the interest of the community and that the particulars of the patients will not be disclosed anyway.

Time Schedule (GANTT CHART):

	1st	2nd	3rd	4th	5th-6th	7th-18th	19th-21st	22nd-23rd	24th
Problem definition									
Literature review									
Research design									
IRB clearance									
Data collection									
Data analysis									
Report writing									
Submission									

5.15 Study flow chart:



5.16 References:

Abreu, A.L.C.S., Soeiro, E.M.D., Bedram, L.G., Andrade, M.C.D. and Lopes, R., 2021. Brazilian guidelines for chronic kidney disease-mineral and bone metabolism disorders in children and adolescents. Brazilian Journal of Nephrology, 43(4 Suppl 1), pp.680-692.

Bhoi, S., Pal, A. and Das, A., 2024.Effect of Calcium and Vitamin D on Bone Health among Kidney Transplant Recipients in a Prospective Randomized Controlled Trial. Indian Journal of Transplantation, 18(3), pp.282-289.

Checa-Ros, A., Locascio, A., Okojie, O.J., Abellán-Galiana, P. and D'Marco, L., 2025.Perirenal fat differs in patients with chronic kidney disease receiving different vitamin D-based treatments: a preliminary study. BMC nephrology, 26(1), p.119.

D'marco, L., Viejo-Boyano, I., Peris-Fernandez, M., Locascio, A. and Checa-Ros, A., 2024.Perirenal fat thickness as a potential marker for cardiovascular risk in chronic kidney disease: the influence of vitamin D analogs. Nephrology Dialysis Transplantation, 39(Supplement_1), pp.gfae069-1460.

Galassi, A., Ciceri, P., Porata, G., Iatrino, R., BoniBrivio, G., Fasulo, E., Magagnoli, L., Stucchi, A., Frittoli, M., Cara, A. and Cozzolino, M., 2021. Current treatment options for secondary hyperparathyroidism in patients with stage 3 to 4 chronic kidney disease and vitamin D deficiency. Expert opinion on drug safety, 20(11), pp.1333-1349.

HabasSr, E., Eledrisi, M., Khan, F., Elzouki, A.N.Y. and Khan, F.Y., 2021. Secondary hyperparathyroidism in chronic kidney disease: pathophysiology and management. Cureus, 13(7).

Holden, R.M., Norman, P.A., Day, A.G., Silver, S.A., Clemens, K.K. and Iliescu, E., 2024. Vitamin D Status and Treatment in ESKD: Links to Improved CKD-MBD Laboratory Parameters in a Real-World Setting. American Journal of Nephrology, 55(6), pp.638-646.

KDIGO, 2017.KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney International Supplements, 7(1), 1–59. https://kdigo.org/guidelines/ckd-mbd/.

Liu, X., Liu, Y., Zheng, P., Xie, X., Li, Z., Yang, R., Jin, L., Mei, Z., Chen, P. and Zhou, L., 2024. Effects of active vitamin D analogs and calcimimetic agents on PTH and bone mineral biomarkers in hemodialysis patients with SHPT: a network meta-analysis. European Journal of Clinical Pharmacology, 80(10), pp.1555-1569.

Magagnoli, L., Ciceri, P. and Cozzolino, M., 2024. Secondary hyperparathyroidism in chronic kidney disease: pathophysiology, Current treatments and investigational drugs. Expert Opinion on Investigational Drugs, 33(8), pp.775-789.

Mathur, A., Ahn, J.B., Sutton, W., Chu, N.M., Gross, A.L., Segev, D.L. and McAdams-DeMarco, M., 2022.Secondary hyperparathyroidism (CKD-MBD) treatment and the risk of dementia. Nephrology Dialysis Transplantation, 37(11), pp.2111-2118.

Muppidi, V., Meegada, S.R. and Rehman, A., 2020.Secondary hyperparathyroidism.

Rodzon-Norwicz, M., Norwicz, S., Sowa-Kućma, M. and Gala-Błądzińska, A., 2023. Secondary hyperparathyroidism in chronic kidney disease: pathomechanism and current treatment possibilities. EndokrynologiaPolska, 74(5), pp.490-498.

Salera, D., Merkel, N., Bellasi, A. and de Borst, M.H., 2025. Pathophysiology of chronic kidney disease–mineral bone disorder (CKD-MBD): from adaptive to maladaptive mineral homeostasis. Clinical Kidney Journal, 18(Supplement_1), pp.i3-i14.

Shah, A., Hashmi, M.F. and Aeddula, N.R., 2024. Chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD). In StatPearls [Internet].StatPearls Publishing.

Stack, B.C., 2024.Secondary hyperparathyroidism. Otolaryngologic Clinics of North America, 57(1), pp.99-110.

Thadhani, R.I., Rosen, S., Ofsthun, N.J., Usvyat, L.A., Dalrymple, L.S., Maddux, F.W. and Hymes, J.L., 2020.Conversion from intravenous vitamin d analogs to oral calcitriol in patients receiving maintenance hemodialysis. Clinical Journal of the American Society of Nephrology, 15(3), pp.384-391.

Yang, G., Huang, Y., Ge, Y., Yu, X., Liu, L., Xiang, L., Liu, B., Gao, C., Liu, C., Xu, Y. and Li, W., 2025. Efficacy and safety of intermittent intravenous doxercalciferol in the treatment of secondary hyperparathyroidism in Chinese patients on maintenance hemodialysis: a phase II, open-label, prospective, multicenter study. Frontiers in Pharmacology, 16, p.1574679.

Part E
Budget:

Sl. No.	Head of expense	
		1st instalment
1	Research tools development	10,000/-
2	Office assistance for organizing the materials	5,000/-
3	Data collection (Investigation cost)	1,50,000/-
4	Drugs Cost	4,44,000/-
5	Data analysis	5000/-
6	Report composing	20,000/-
7	Printing	5,000/-
8	Stationaries	5,000/-
9	Transport/conveyance	1000/-
10	Miscellaneous	5000/-
	Total amount	**6,40,000/-**

Appendix
Case record form

Protocol Title: "Effects of Doxercalciferol Compared to Calcitriol For Lowering Parathyroid Hormone Level in Patients on Hemodialysis."

Patient's identification			
1	Patient ID No.		
2	Contact no:		
3.	Group: **Group 1:**Experimental Group **Group 2:**Control Group		
Demographic characteristics			
1	Age:	……..…years	
2	Sex:	0=Female 1=Male	
3	Group:	1=Group 1, 2=Group 2	
4	Monthly Income:	……..…BDT	
5	Height:	……..…cm	
6	Weight:	……..… kg	
7	BMI:	……..… kg/m²	
Clinical Variables			
1	Primary disease of CKD:	1=GN,2=DM,3=HTN,4=Others	
2	Duration of CKD diagnosis:	……years	
4	Blood Pressure:	……..…… mmHg	
5	Duration of Hemodialysis:	……..…… months/years	
Baseline Biochemical Variables			
1	Serum Calcium (S. Ca):	……..…… mg/dL	
2	Serum Phosphate (Po4):	……..…… mg/dL	
3	Parathyroid Hormone (PTH):	……..……pg/mL	
Follow-up at 12 Weeks			
1	Serum Calcium (S. Ca):	……..…… mg/dL	
2	Serum Phosphate (Po4):	……..…… mg/dL	
3	Parathyroid Hormone (PTH):	……..……pg/mL	

	Adverse Effect		6 weeks	12 weeks
1	Nausea	N0= 0 Yes= 1		
2	Vomiting	N0= 0 Yes= 1		
3	Edema	N0= 0 Yes= 1		
4	Headache	N0= 0 Yes= 1		
5	Fatigue	N0= 0 Yes= 1		
6	Matallic test	N0= 0 Yes= 1		
7	Loss of appetite	N0= 0 Yes=1		
8	Constipation	N0= 0 Yes= 1		
9	Withdrawal	N0= 0 Yes= 1		
10	Expired	N0= 0 Yes= 1		
11	Others	N0= 0 Yes= 1		

Outcome

	Complete the study per the Protocol 0= No 1= yes
	If not reason for drop-out 1. Adverse experience 2. Failure to return for follow-up 3. Patients refuse treatment 4. Patient died 5. Non-co-operation 6.Insufficient therapeutic response

Signature of the researcher: **Signature of the Guide/Co-guide**

Consent form

"Effects of Doxercalciferol Compared to CalcitriolFor Lowering Parathyroid Hormone Level in Patients on Hemodialysis"

After being fully informed about the objectives, consequences of the study and any right to withdraw me from the study at any time for any purpose whatsoever, I am ---------- at this moment giving consent to participate in the study conducted by DR. A.K.M. Arshadul Abbas, MD (Nephrology) Phase-B student, Chittagong Medical College.

I fully recognize that my participation in this study will generate valuable medical information that might be used for the interest of patients in future.

In this research, if any adverse effects of drugs are found, investigators will take immediate measures for treatment.

I shall try my best to comply with the instruction given by the investigator throughout the whole period of study.

Signature/ Thumb impression.....
of the subject
Date.....

Signature/ Thumb impression….
of the patient's guardian
Date……

Signature /Thumb impression
Of the witness
Date.....

Signature of the investigator
Date…..

Informed Consent Form

Research approval number: _ _ _ _ _ _ _

Title of Research: **Effects of Doxercalciferol Compared to Calcitriol For Lowering Parathyroid Hormone Level in Patients on Hemodialysis.**
Name and researcher affiliation: This study is conducted by DR. A.K.M. Arshadul Abbas, Department of Nephrology, Chittagong Medical College.

1. About the study:

I have decided to do a Thesis for MD (Nephrology) Phase B examination on "Effects of intravenous Doxercalciferol for lowering PTH compare to that of oral calcitriol in hemodialysis patients" After receiving your written consent, I want to include you as a research participant. I will explain to you briefly what the components are and your role in the research.

2. Purpose and nature of the research:

The purpose of this research is to compare the effectiveness of intravenous doxercalciferol versus oral calcitriol in lowering parathyroid hormone (PTH) levels among hemodialysis patients. This study will evaluate the biochemical responses to both treatments, aiming to identify a superior therapeutic approach. The research is analytical and interventional in nature, involving direct clinical intervention and subsequent measurement of outcomes over a follow-up period.

3. Selection of the participant: As you are diagnosed with hemodialysis patients with secondary hyperparathyroidism, you are selected as a research subject. However, only the patients who provide written informed consent will be included.

4. Privacy, anonymity, and confidentiality:

Collected information will be kept confidential unless permitted by you. This information will be used only for research purposes. Your data will not be disclosed to anyone.

5. Right to refuse or withdraw:

You have all the right to refuse to participate in this research if you do not wish to do so, and rejecting to participate will not affect your treatment. You may stop participating in this research whenever you want to without show any reason and without losing any rights as a patient here.

6. What are the risks/or discomfort in the research?

The research will be observational. So, there will be no additional physical risk or discomfort from being in this research.

7. Incentives:

You will not be provided with any incentives to take part in the research.

8. Benefits:

You will get direct benefits from participation in the study, as a detailed biochemical assessment will be done free of cost.

9. The researcher's responsibility:

I will act only as a researcher, and the respective doctors of the hospital will carry out your treatment.

10. Procedure of research:

If you agree, we will enroll your relative as a research participant and will adopt the following procedures for your participation-

i. We will take your signature/thumb impression from you in the attached consent form in duplicate, and a copy will be returned to you.

ii. We will ask some questions about your disease, perform a basic physical examination, and fill out a printed record form.

If you agree to participate in the research, please sign this form.

Appendix

Data and Safety Monitoring Board

"Effects of Doxercalciferol Compared to CalcitriolFor Lowering Parathyroid Hormone Level in Patients on Hemodialysis"

Name of the researcher. This study is being conducted by Dr. A.K.M. Arshadul Abbas, Phase-B Resident, MD (Nephrology), Department of Nephrology, Chittagong Medical College.

Place of the study: Department of Nephrology, Chittagong Medical College Hospital, Chattogram.

Type of Study: Randomized Controlled Trial

Members of the board:

----------Professor, Department of Nephrology Chittagong Medical College and Hospital, Chattogram, Bangladesh

----------professor. Department of Medicine, Chittagong Medical College and Hospital, Chattogram, Bangladesh

----------Assistant professor, Department of Nephrology, Chittagong Medical College and Hospital, Chattogram, Bangladesh

DATA AND SAFETY MONITORING PLAN

Once a protocol is referred to the data and safety monitoring committee (DSMC). The first steps for the principle investigator to develop a Data and Safety Monitoring Plan (DSMP) A DSMP is a written plan that specifies a system for appropriate study oversight to ensure: (1) safety of clinical research subjects, (2) validity and integrity of research data, and (3) appropriate termination study. Once the plan elements listed here are submitted to the DSMC, the DSMC will work with the investigator to finalize the plan and assure that it is implemented.

Enrollment of the study participants by months:

Month	Approached	Eligible	Randomized	Withdrawn	Actual #	Cumulative #
1						
2						
3						
4						

Subject Status:

Patient ID	Date enrolled	Date completed	Status (Active/ completed / Withdrawn)	Reason of withdrawal	Adherence	Intervention duration
1						
2						
3						
4						

Adverse events (AE) Patient ID

Patient ID	AE Onset	AE End	Severity	Related to intervention	Action taken	Outcome	Comment
1							
2							
3							
4							

Appendix

Withdrawal Form

“Effects of Doxercalciferol Compared to CalcitriolFor Lowering Parathyroid Hormone Level in Patients on Hemodialysis”

1----------myself thesis case no...----------of Dr. A.K.M Arshadul Abbas Hereby I withdraw myself/ my patient from signed protocol of treatment. I will continue the treatment of myself/my patient according to standard protocol.

Name---------- Signature/Thumb Impression: ----------

Name of Witness:----------Signature/Thumb Impression:----------

Date:----------

Name & Signature of researcher----------