TITLE OF THE STUDY- EFFECT OF DAPAGLIFLOZIN COMPARED TO DAPAGLIFLOZIN-FINERENONE COMBINATION ON ALBUMINURIA IN PATIENTS WITH CHRONIC KIDNEY DISEASE AND TYPE 2 DIABETES: A RANDOMIZED CONTROLLED TRIAL.

NCT number- N/A

Date of the document- 29.04.2026

THESIS PROTOCOL

TITLE

EFFECT OF DAPAGLIFLOZIN COMPARED TO DAPAGLIFLOZIN-FINERENONE COMBINATION ON ALBUMINURIA IN PATIENTS WITH CHRONIC KIDNEY DISEASE AND TYPE 2 DIABETES: A RANDOMIZED CONTROLLED TRIAL.

INVESTIGATOR:

Dr. Debasis Roy

Resident

MD (Nephrology) Phase-B

Session: March, 2024

GUIDE:

Prof. Dr. Md Nurul Huda

MBBS, MCPS (Medicine), FCPS (Medicine),
MD (Nephrology), FASN
Professor and Head,
Department of Nephrology,
Chittagong Medical College and Hospital

CO-GUIDE:

Dr. Rafiqul Hasan
MBBS,MCPS(Medicine), FCPS (Medicine),
MD (Nephrology)Associate 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, "Effect of dapagliflozin compared to dapagliflozin-finerenone combination on albuminuria in patients with chronic kidney disease and type 2 diabetes: A randomized controlled trial."

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. Debasis Roy
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. Debasis Roy**
2.	Course	:	MD (Nephrology-Phase B)
3.	Category	:	Government
4.	Title of the study	:	Effect of dapagliflozin compared to dapagliflozin - finerenone combination on albuminuria in patients with chronic kidney disease and type 2 diabetes: A randomized controlled trial.
5.	Type of the study	:	Randomized,open-label,active controlled trial
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. Md Nurul Huda Professor and Head, Department of Nephrology, Chittagong Medical College and Hospital, Chattogram, Bangladesh
10.	Name of the Co-Guide	:	Dr. Rafiqul Hasan MBBS,MCPS(Medicine), FCPS (Medicine), MD (Nephrology) Associate 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. Debasis Roy
MD (Nephrology-Phase B)
Department of Nephrology
Chittagong Medical College and Hospital
Chattogram, Bangladesh

Forwarding from the Guide

……
Guide

Prof. Dr. Md Nurul 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. Debasis Roy
2.	Course	:	MD (Nephrology Phase B)
3.	Category	:	Government
4.	Title of the study	:	Effect of dapagliflozin compared to dapagliflozin - finerenone combination on albuminuria in patients with chronic kidney disease and type 2 diabetes: A randomized controlled trial.
5.	Type of the study	:	Randomized,open-label,active controlled trial
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. Md Nurul Huda, Professor and Head, Department of Nephrology, Chittagong Medical College and Hospital, Chattogram, Bangladesh
10.	Name of the Co-Guide	:	Dr. Rafiqul Hasan Associate 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	:	Effect of dapagliflozin compared to dapagliflozin - finerenone combination on albuminuria in patients with chronic kidney disease and type 2 diabetes: A randomized controlled trial.
2.	Name of the applicant	:	Dr. Debasis Roy
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	:	**= 5,66,000/-**
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. Debasis Roy
   Designation : Student, MD (Nephrology Phase B)
   Official address with telephone & mail : Department of Nephrology, Chittagong Medical College Hospital, Chattogram
   Phone:01737376811
   Email: debasisroy2014@gmail.com
   Present residential address : C/O. Mr. Alamgir
   Battery Lane, Kazir Dewari, Dampara, Chattogram.
2. Academic Background :

Degree	**Institute**	**University/Board**	**Field**	**Year**
M.B.B.S	Chittagong Medical College	Chittagong University	Passed	2011

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: Effect of dapagliflozin compared to dapagliflozin-finerenone combination on albuminuria in patients with chronic kidney disease and type 2 diabetes: A randomized controlled trial.

Summary

Background: Chronic kidney disease (CKD) in individuals with type 2 diabetes (T2D) is a major global health concern, often marked by persistent albuminuria. Mineralocorticoid receptor antagonists finerenone have shown promise in reducing albuminuria and slowing renal decline. Concurrently, sodium-glucose cotransporter-2 inhibitors like dapagliflozin have demonstrated significant nephroprotective benefits. The interplay of these therapeutic classes in diabetic nephropathy suggests potential additive or synergistic effects. Dapagliflozin combined with finerenone, is claimed to have more effectiveness in reducing albuminuria compared to dapagliflozin monotherapy.

Aims: The study aims to evaluate the effect of dapagliflozin combined with finerenone compared to dapagliflozin alone on albuminuria in patients with chronic kidney disease and type 2 diabetes.

Materials and Methods: This open-label randomized controlled trial will be conducted in the Department of Nephrology of Chittagong Medical College Hospital, Chattogram, Bangladesh including 88 patients with chronic kidney disease and type 2 diabetes. Participants will be randomized into one of two study groups. The experimental group will be treated with dapagliflozin 10 mg plus finerenone 10 mg once daily for eight weeks. The control group will receive dapagliflozin 10 mg once daily for the same duration. The primary outcome measure will be the change in UACR, while the other variables will include serum creatinine, eGFR, serum potassium. Adverse events and safety measures will also be recorded. The primary analysis will follow either an intention-to -treat or a perprotocol approach and will be performed using SPSS version 27.

Conclusion: This study will elucidate the efficacy and safety of dapagliflozin - finerenone combination in a Bangladeshi cohort, potentially guiding strategies to mitigate albuminuria in T2DM.

PART-D

1. Introduction:

Chronic kidney disease is a common and serious complication in individuals with type 2 diabetes, contributing significantly to morbidity and mortality. It progresses silently and is frequently associated with increased cardiovascular risks and reduced renal function (Navaneethan et al., 2025; Hansrivijit et al., 2025).

The global prevalence of chronic kidney disease (CKD) among patients with type 2 diabetes mellitus (T2DM) is a growing concern, with approximately 27% of diabetic individuals affected worldwide according to a recent meta-analysis (Fenta et al., 2023). Regional studies further highlight this burden; in the United States, CKD prevalence among T2DM patients rose to 1.28% by 2018 (Feng et al., 2021). In Ethiopia, prevalence estimates vary significantly, reaching 31.5% in South Wollo (Adem et al., 2024) and 14.3% in Northwest regions (Alemu et al., 2020). Recent studies from Bangladesh according to Mahbub et al. (2024), the prevalence of CKD among T2DM patients in selected hospitals in Dhaka was found to be 34.5%, highlighting a critical public health issue. This aligns with global estimates but emphasizes regional variation due to socioeconomic, environmental, and healthcare access factors. These disparities reflect underlying differences in healthcare access, screening practices, and comorbid conditions, underscoring the need for targeted interventions and enhanced surveillance globally.

Chronic kidney disease (CKD) in patients with type 2 diabetes mellitus (T2DM) is closely associated with increased cardiovascular morbidity and premature mortality, with cardiovascular disease remaining the leading cause of death in this population (Zannad et al., 2024). Despite current therapies, a substantial proportion of patients continue to progress to end-stage kidney disease, necessitating urgent refinement of treatment approaches (Rossing et al., 2022).

Albuminuria reflects glomerular damage and serves as a strong predictor of chronic kidney disease (CKD) progression and cardiovascular morbidity. Elevated urinary albumin-to-creatinine ratio (UACR) indicates a disrupted filtration barrier, contributing to nephron loss via inflammation and fibrosis. Both SGLT2 inhibitors

and mineralocorticoid receptor antagonists (MRAs) reduce albuminuria by restoring tubuloglomerular feedback and reducing intrarenal inflammation, respectively (Hanouneh et al. 2024; Provenzano et al. 2022). Albuminuria reduction is not only a marker of therapeutic efficacy but also correlates with better renal outcomes, making it a valuable surrogate endpoint in clinical trials (Provenzano et al. 2022). Notably, combined therapy offers an additive reduction in UACR, enhancing nephroprotection beyond monotherapy (Hanouneh et al. 2024; Provenzano et al. 2022). Thus, albuminuria serves both as a mechanistic insight into CKD pathogenesis and a clinically meaningful surrogate to monitor therapeutic impact.

Sodium-glucose cotransporter-2 inhibitors (SGLT2is) have emerged as vital agents in slowing the progression of chronic kidney disease (CKD), particularly in individuals with type 2 diabetes (T2D). Their renoprotective effects stem from reductions in albuminuria, improved glycemic control, and favorable hemodynamic and anti-inflammatory effects (Green et al. 2023; Provenzano et al. 2022). Dapagliflozin, a selective SGLT2i, was chosen in the DAPA-CKD trial for its demonstrated ability to reduce kidney failure and cardiovascular risk in both diabetic and non-diabetic CKD populations (Provenzano et al. 2022). Its consistent efficacy across subgroups, including those concurrently treated with mineralocorticoid receptor antagonists (MRAs), further supports its role in combination therapy strategies. Moreover, dapagliflozin's ability to mitigate hyperkalemia risk, a common concern with MRAs, enhances its clinical appeal (Provenzano et al. 2022). The dual benefit of cardiovascular and kidney protection underpins its integration into CKD management paradigms (Green et al. 2023; Provenzano et al. 2022).

Finerenone is a non-steroidal, selective MRA with greater receptor selectivity and anti-inflammatory and anti-fibrotic effects, resulting in reduced incidence of hyperkalemia and broader tissue distribution than steroidal agents like eplerenone (Kim et al. 2023, Barrera-Chimal et al. 2022, Sarafidis et al. 2023). Unlike eplerenone, which has a longer half-life and active metabolites, finerenone offers shorter systemic exposure and minimal interaction with steroid receptors, improving safety in CKD (Sarafidis et al. 2023).Clinical trials, including FIDELIO-DKD and

FIGARO-DKD, demonstrated that finerenone significantly delays CKD progression and reduces cardiovascular events compared to placebo, even when added to optimized renin-angiotensin system blockade (Rossing et al. 2022, Barrera-Chimal et al. 2022). Meta-analyses have confirmed finerenone's superior efficacy, especially when combined with SGLT2 inhibitors, showing additive benefits on albuminuria and cardiovascular protection (Ferreira et al. 2024). These distinctions position finerenone as a preferred MRA in diabetic CKD management strategies.

Consequently, both SGLT2i and finerenone are now endorsed in guidelines as standard therapies for CKD associated with T2D (de Boer et al., 2022). Clinical evidence indicates that combining MRAs with SGLT2i yields greater reductions in albuminuria and blood pressure compared to SGLT2i monotherapy, while SGLT2i may counterbalance the hyperkalemia risk associated with MRAs, enhancing the safety profile of dual therapy (Ferreira et al., 2024). However, direct comparisons between SGLT2i monotherapy and in combination with finerenone remain scarce, particularly in Bangladeshi populations. Ethnic variations in drug metabolism, dietary potassium intake, and genetic predispositions to electrolyte imbalances underscore the need for region-specific data to optimize therapeutic strategies. Additionally, the impact of these regimens on albuminuria—a validated surrogate marker for long-term renal outcomes—has not been comprehensively explored, limiting insights into early treatment efficacy. This study aims to address these gaps by investigating the efficacy and safety of dapagliflozin alone and in combination with finerenone in reducing albuminuria among Bangladeshi patients with CKD and type 2 DM.. The findings may guide clinical decision-making by clarifying whether dual therapy offers superior early albuminuria reduction compared to SGLT2i monotherapy, while balancing risks such as hyperkalemia and eGFR fluctuations.

2. Rationale

Emerging evidence suggests that combining SGLT2i with MRAs may yield additive reno-protective effects and further reduces albuminuria while mitigating hyperkalemia. However, head-to-head comparisons between dapagliflozin alone and its combination with finerenone, remain scarce. Bangladesh, with its high T2DM burden and limited access to advanced renal therapies, requires evidence to optimize safe dual therapies for diabetic nephropathy. This study addresses these gaps by evaluating albuminuria reduction and safety of dapagliflozin alone and its combination with finerenone in a Bangladeshi cohort.

3. Research question/Hypothesis:

3.1 Research question: Is dapagliflozin-finerenone combination effective as dapagliflozin alone in reducing albuminuria in patients with chronic kidney disease and type 2 diabetes?

3.2 Research hypothesis: Dapagliflozin-finerenone combination is more effective than dapagliflozin alone in reducing albuminuria in patients with chronic kidney disease and type 2 diabetes.

4. Objectives

4.1 General objective:

To evaluate the effect of dapagliflozin-finerenone combination on albuminuria in patients with chronic kidney disease and type 2 diabetes compared to dapagliflozin alone.

4.2 Specific Objectives:

1. To compare the change in urinary albumin-to-creatinine ratio (UACR) from baseline to the end of the study between dapagliflozin - finerenone combination group and dapagliflozin alone group.
2. To compare the changes in serum potassium levels between the two groups during the study period.
3. To estimate and compare the changes of eGFR between the two groups.
4. To evaluate the proportion of patients achieving a clinically significant reduction in albuminuria (e.g., ≥30% decrease in UACR) in each groups.
5. To evaluate the overall safety and tolerability profiles of the combination therapy compared to dapagliflozin monotherapy.

5. Materials and method:

5.1. Type of study: Randomized, open-label, active controlled trial.

5.2 Place of **Study**: Department of Nephrology, Medicine and Endocrinology & Metabolism, Chittagong Medical College Hospital, Chattogram, Bangladesh.

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

5.4 Study population: Adults with chronic kidney disease and type 2 diabetes attending the Nephrology, Medicine and Endocrinology & Metabolism outdoors at CMCH will be the study population during the study period.

5.5 Study groups: Based on the interventions, there will be two groups in the study

1. Experimental group: Dapagliflozin 10 mg plus finerenone 10 mg

2. Control group : Dapagliflozin 10 mg alone

5.6 Sampling technique: Consecutive patients attending the Nephrology, Medicine and Endocrinology & Metabolism Departments at CMCH will undergo screening based on predefined inclusion and exclusion criteria. Eligible participants will be randomly allocated (via computer-generated randomization) to one of the two treatment arms.

5.7 Inclusion criteria:

- Patients aged $\geq$ 18 years
- Patients with T2 DM , as defined by the American Diabetic Association.
- Urinary ACR $\geq$ 30 mg/g and eGFR $\geq$ 25 ml/min per 1.73 m2
- Prior treatment with ACEIs or ARBs for more than four weeks up to the maximum tolerated dose
- Serum potassium $\leq$ 4.8 mmol/L

5.8 Exclusion criteria

- Patients with other known causes of proteinuria, e.g. UTI, fever
- At screening visit SBP higher than 160 mmHg or DBP higher than 100 mmHg or SBP lower than 90 mmHg
- Glycated hemoglobin (HbA1C) >11%
- Known hypersensitivity to dapagliflozin or finerenone
- Known case of Addison's disease
- Known case of hepatic insufficiency
- Treatment with SGLT2i (empagliflozin:62 hours, dapagliflozin:65hours) or MRAs (finerenone:10-20 hours, spironolactone:7 hours , eplerenone:15-30 hours) within their wash out periods.
- Patients on non-dihydropyridine Calcium Chanel blockers or Glucagon-like peptide-1 (GLP-1) agonists
- Pregnant lady or lactating mother

5.9. Sample size: Sample size calculation for hypothesis testing of difference between two proportions:

$$n = \frac{p(100-p) + q(100-q)}{(p-q)^2}\left(z_\alpha + z_\beta\right)^2$$

Where,

Z_α = Z value of standard normal distribution at a definite level of significance

Z_β = Z value of standard normal distribution at a definite level of power

p = Percent change from baseline in UACR after treatment in the experimental group

q= Percent change from baseline in UACR after treatment in the control group

Here,

$Z_\propto$= 1.96 at 95% Confidence Interval

Z_β =1.28 at 90% power

p = 36% (Mårup et al., 2024)

q= 8% (Mårup et al., 2024)

So,

$$n = \frac{36\,(100-36)+8(100-8)}{(36-8)^2}(1.96+1.28)^2 \approx 40$$

Considering 10% lost to follow-up final sample will be $(40 + 40 \times 10\%) = 44$. That means 44 patients in each group will be needed to test the hypothesis.

5.10 List of Variables

Demographic Variables

Variables	Type	Value	Expression
Age	Discrete	In completed years	Mean ± SD
Sex	Categorical	Male / Female	Frequency (%)
Monthly income	Continuous	In local currency (BDT)	Mean ± SD /Median (IQR)

Clinical Variables

Variables	Type	Value	Expression
Duration of diabetes	Discrete	In years	Mean ± SD
Duration of HTN	Discrete	In years	Mean ± SD
Current medication for DM	Categorical	Insulin/Oral Hypoglycemic Agents/Both	Frequency (%)
Current medication for HTN	Categorical	ACE inhibitor/ARB/MRAs/Beta-blocker/Calcium channel blocker/Diuretics/Others	Frequency (%)
Blood pressure	Continuous	In mm Hg	Mean ± SD
Height	Continuous	Meter	Mean ± SD
Weight	Continuous	Kg	Mean ± SD
BMI	Continuous	kg/m^2	Mean ± SD
Adverse events	Categorical	Present / Absent	Frequency (%)

Biochemical Variables

Variables		Type	Value	Expression
UACR		Continuous	mg/g	Mean ± SD
eGFR		Continuous	mL/min/1.73 m²	Mean ± SD
Serum creatinine		Continuous	mg/dL	Mean ± SD
Serum potassium		Continuous	mmol/L	Mean ± SD
Fasting blood glucose		Continuous	mg/dL	Mean ± SD
2 hour postprandial blood glucose		Continuous	mg/dL	Mean ± SD
HbA1C		Continuous	Percent (%)	Mean ± SD
Urinalysis	Albumin	Categorical	-/trace/+/++/+++/++++	Frequency (%)
	RBC	Discrete	..... /HPF	Mean ± SD
	WBC	Discrete	..... /HPF	Mean ± SD

5.11 . Operational definitions:

A. CKD : According to 2024 KDIGO guideline for CKD , CKD is defined as abnormalities of kidney structure or function, present for a minimum of 3 months, with implications for health . Criteria for chronic kidney disease (either of the following present for a minimum of 3 months)

1. Markers of kidney damage (1 or more):

a. Albuminuria (ACR ≥ 30 mg/g [≥3 mg/mmol])

b. Urine sediment abnormalities

c. Persistent hematuria

d. Electrolyte and other abnormalities due to tubular disorders

e. Abnormalities detected by histology

f. Structural abnormalities detected by imaging

g. History of kidney transplantation

2 . Decreased GFR : GFR <60 ml/min per 1.73 m2 **(GFR** categories G3a-G5)

B. Diabetes Mellitus: Previously diagnosed Diabetic patients on insulin or oral antidiabetic drug or those having Fasting blood glucose ≥7 mmol/l (126 mg/dl) or Postprandial glucose ≥11.1 mmol/l (200 mg/dl) during OGTT or HbA1C ≥ 6.5%.(ADA, 2010)

C. eGFR: The CKD-EPI equation, expressed as a single equation, is:

- $GFR = 141 \times \min(Scr/\kappa,1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black]

Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

D. Diabetic Nephropathy: Diabetic patients with urinary albumin excretion >30 mg/g on at least two occasions three months apart and no other kidney or renal tract disease.(Tuttle et al., 2014)

E. Genital and perineal hygiene : Patient education about genital and perineal hygiene should be taken as a preemptive measure for all the diabetic patients irrespective of the antidiabetic therapy. This should include washing of genital organs followed by urination or defecation, routine hygienic wipes or sprays, women should be advised to wash from front-to-back, uncircumcised males should retract the prepuce before wash, use clean water for washing or mild soap if required, alcohol-based disinfectant should not be used for washing.(Unnikrishnan et al., 2018)

F. Withdrawal criteria

1. A sustained decrease in eGFR to <15 mL/min/1.73 m2 or sustained decrease in eGFR ≥40% compared to baseline over ≥4 weeks was defined by evidence of ≥2 consecutive laboratory assessments or need to start dialysis (Bakris et al., 2020)
2. Persistently high potassium level ≥5.5 mmol/l even after holding Finerenone for 3 days and adjusting other diet and medications.
3. If patient develops diabetic ketoacidosis (DKA) including euglycemic DKA. DKA will be defined as blood glucose >11.1 mmol/L,urine ketone bodies more than 2+ on dipstick testing and a serum bicarbonate level <15 mmol/L.
4. If patient develops symptoms and signs suggestive of Fournier's gangrene (pain, swelling, erythema, foul-smelling discharge or necrosis) in the perineal or genital area.
5. Drug intolerance or patient refusal to continue medication due to adverse effects like dizziness, arthralgia etc.
6. The patient wants to withdraw himself from the study
7. If any participant becomes pregnant during the study period

G. Adverse Events: (AE)

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. The most common adverse event of finerenone is hyperkalemia. Other common adverse events are decreased GFR, hypotension, back pain, dizziness, arthralgias, constipation. The most common adverse events of dapagliflozin is genital mycotic infection. Other adverse events are urinary tract infection, hypotension, hypoglycemia, acute kidney injury, DKA, Fournier's gangrene.

Major adverse events will be defined as any event leading to admission or prolonged admission, withdrawal, or death.

Minor adverse events will be defined as minor if it does not require admission to the hospital or withdrawal of the drug.

Drug intolerance refers to the inability to tolerate the adverse effects of medication at a therapeutic or substantial dose.

H. Treatment Compliance :Compliance to study treatment, calculated as ([overall amount of dose actually taken] / [overall expected amount of dose to be taken]) × 100%, was also assessed (on-treatment + 7 days analysis set, *i.e.,* all patients who received one dose of study treatment and censored at 7 days after treatment discontinuation). The dose taken was based on medication returned by patients to their clinics. Adequate treatment compliance was defined as ≥75%, and significant noncompliance was defined as <50%. (Carolina, 2023)

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

5.13 Data collection procedure:

Baseline evaluation: Patients with chronic kidney disease and type 2 diabetes will be screened consecutively and prospectively by the above inclusion and exclusion criteria to select eligible patients. Eligible patients and their legal relatives will be fully explained the study protocol, their role in the study, and the risk of the study. They will be enrolled in the study after getting written informed consent. Demographic and clinical information will be collected as per the case record form by interviewing the patients, reviewing the medical records, and performing physical examinations. After taking proper history and physical examinations, blood and urine samples will be collected for biochemical analysis. Blood tests will include measurement of Serum Creatinine, Estimated Glomerular Filtration Rate (eGFR), Serum Potassium, Fasting Blood Sugar (FBS), 2-Hour Postprandial Blood Sugar (2HPPBS) and HbA1C. Urine samples will be analyzed for Urine Albumin-Creatinine Ratio (first morning urine) and routine examination (R/E), including albumin, RBC and WBC. If a patient reports symptoms or any biochemical findings suggestive of a Urinary Tract Infection (UTI), a urine culture and sensitivity (C/S) test will be performed. Baseline clinical and laboratory parameters will be recorded in the case record form.

Radomization: Once a participant is enrolled in the study and consents to participate, they will be assigned to a treatment group according to the randomization sequence. Patients will be randomly assigned to either experimental groups or control group with a 1:1 ratio (block size of four). Randomization will be carried out using online software (Research Randomizer Version 4.0 at https://www.randomizer.org).

Blinding: The study will be open-label, with both participant and the researcher aware of their treatment allocation.

Treatments: The treatment phase lasted for eight weeks. The experimental group will receive oral dapagliflozin 10 mg plus Finerenone 10 mg daily. While the control group will receive oral dapagliflozin 10 mg daily. All the patients will be advised to follow standard dietary advice (including low salt <5gm/daily, diabetic diet), regular exercise, regular home capillary glucose monitoring & maintain all the standard pharmacological therapies throughout the study, including oral antidiabetic drug/insulin and any other antihypertensive medications (if required).

Evaluation of patients at 4 weeks: The patients will be followed up at 4 weeks. The physical examinations will be done, and the following parameters will be measured at follow-up: Serum creatinine, eGFR, serum potassium, FBS, 2HPPBS, Urine R/E and Urinary ACR. The patients will be instructed to report immediately in case of any adverse events following consumption of the drugs. If a patient develops symptoms or signs suggestive of genital mycotic infection (itching, erythema, discharge), a culture and sensitivity (C/S) test of vaginal discharge (in female) or penile swab (in male) will be performed. Tolerability will be assessed by employing an adverse event profile (adverse events, serious adverse events). Safety will be evaluated based on the incidence of A/E. The safety population consists of subjects who receive at least one dose of study medication. Necessary action will be taken for any adverse effect complained by participants.

Evaluation of patients at 8 weeks and outcome assessment: All the patients will be evaluated at 8 weeks again. Physical examination will be done. Biochemical parameters will be reassessed, including Serum Creatinine, eGFR, Serum Potassium, FBS, 2HPPBS, urine R/E and urinary ACR. 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, and ask that the patient return for a final visit, if applicable, and follow up with the patient regarding any unresolved adverse events

In every visit, for blood test, blood will be collected from accessible vein with proper aseptic precaution and patient remained at least 8 hours overnight fasting before blood collection and blood was collected into red topped vacutainer. After collection of 10 mL blood, it will be allowed to clot by leaving it undisturbed at room temperature for 10-15 minutes and will removed the clot by centrifuging at 3000rmp for 10 minutes for serum. Serum creatinine concentration will be measured by buffer kinetic jeffe reaction using a SIEMENS dimension EXL200 analyzer while eGFR will be measured by CKD-EPI formula. The urinary albumin concentration was determined using a nephelometry method by BN pro-spec analyzer while urinary creatinine concentration was measured by endpoint spectrophotometric method with an alkaline picrate solution using a SIEMENS dimension EXL200 analyzer. UACR will be calculated by dividing the concentration of urinary albumin by the concentration of urinary creatinine. All the investigations will be performed in an ISO certified laboratory.

5.14. Data analysis:

Data will be recorded in the form of an Excel worksheet. After completion of data collection, data will be analyzed using the Statistical Package for Social Sciences (SPSS) version 27.0 (IBM Corp., Armonk, NY, USA).The continuous variables will be presented by measures of central tendency and measures of dispersion. For the normally distributed data, mean ± standard deviation will be used, and for non-parametric data, median and Interquartile range (IQR) will be presented. On the other hand, we would present the categorical variables as frequency distribution. Between groups, comparisons of independent variables will be performed by independent t-test and Mann-Whitney U-test for normally and not-normally distributed variables respectively. Within patients, comparison will be performed by paired t-test or Wilcoxon Signed Rank Test, as appropriate. The Chi-square test will investigate the differences in categorical variables between two groups. Repeated measures ANOVA will be performed to compare mean values across multiple time points within the same group. Where appropriate, post-hoc analysis with Bonferroni correction will be conducted to identify specific time points with significant difference. A p-value <0.05 will be considered statistically significant.

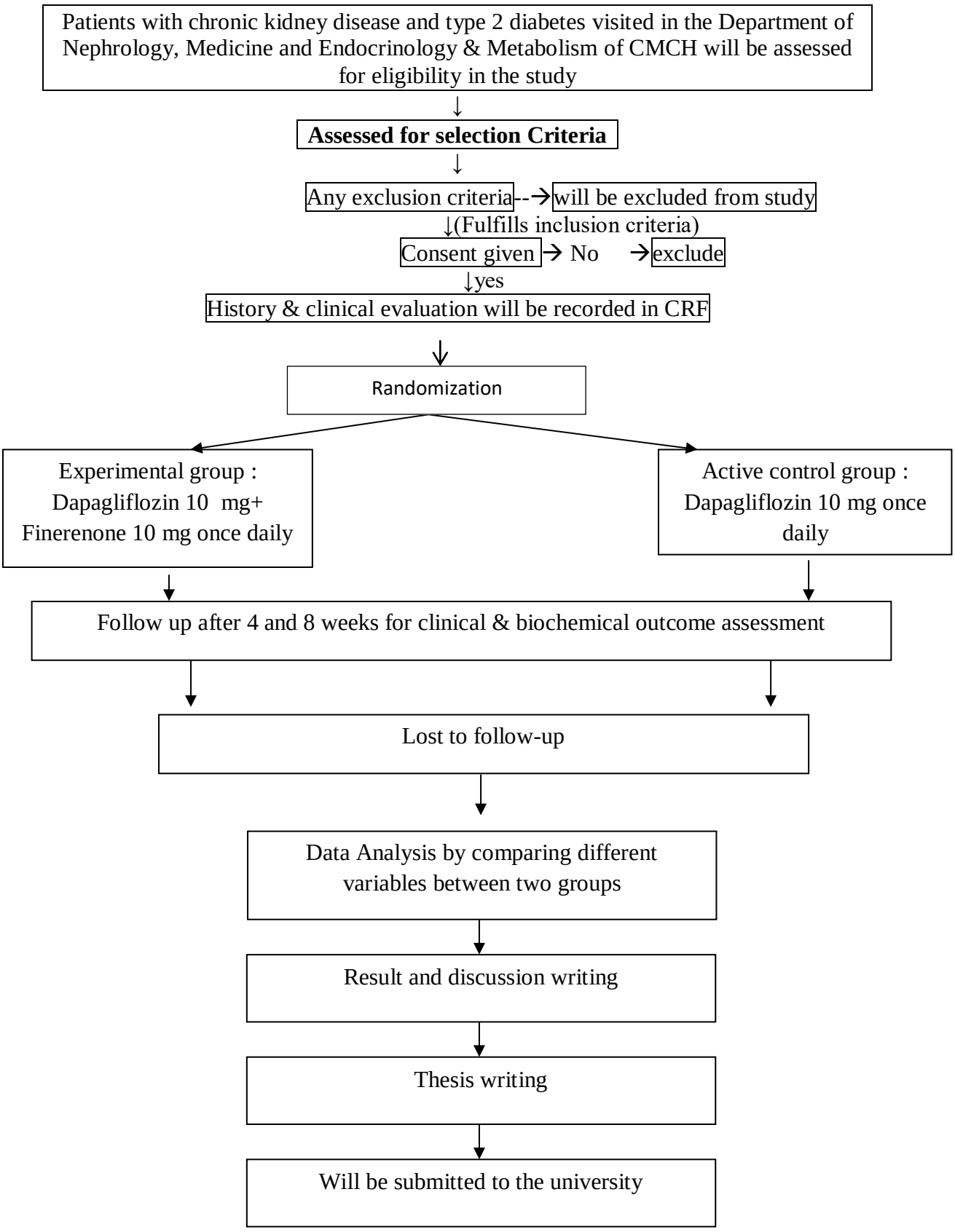
5.15. The utilization of results: This trial will provide critical evidence on the efficacy and safety of dapagliflozin-finerenone combination in a resource-limited setting, addressing a significant unmet need in the management of DN. Every effort will be made to publish the results in peer-reviewed national and international journals. The results of this study will be published as a thesis and submitted to the corresponding university as MD (Nephrology) exam requirement. The result of the study will be presented to the Department of Nephrology, CMCH.

5.16. 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. 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.

5.17 TIME SCHEDULE (GANTT CHART)

	1st	2nd	3rd	4th	5th -6th	7th-18th	19th-21th	20th-23th	24th
Problem definition									
Literature review									
Research design									
IRB clearance									
Data collection									
Data analysis									
Report writing									
Submission									

5.18 Study flow chart:



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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)	3,00,000/-
4.	Drug cost	2,00,000/-
5.	Data analysis	5,000/-
6.	Report composing	30,000/-
7.	Printing	5,000/-
8.	Stationaries	5,000/-
9.	Transport/conveyance	1,000/-
10.	Miscellaneous	5,000/-
	Total amount	**5,66,000/-**

Appendix

Case record form

Protocol Title: Effect of dapagliflozin compared to dapagliflozin-finerenone combination on albuminuria in patients with chronic kidney disease and type 2 diabetes: A randomized controlled trial.

Patient's identification				
1	Patient ID No.			
2	Name of the patient			
3	Contact no:			
4	Address:			
5	Study group: **Group 1: Experimental group** **Group 2:** Control group			
Demographic characteristics				
1	Age:	……..…years		
2	Sex:	0=Female 1=Male		
3	Place of residence	1=Urban, 0= Rural		
3	Monthly income	……BDT		
Clinical Characteristics				
1	Duration of Diabetes Mellitus	……..…… years		
2	Duration of Hypertension	……..…… years		
3	Current medication for DM	1=Insulin 2=Oral Hypoglycemic Agents 3=Both Insulin and Oral Hypoglycemic Agents		
4	Current medication for HTN	1=ACEi, 2=ARB, 3=MRA, 4=Beta blocker, 5=CCB, 6=Diuretics, 7=Others		
Clinical Parameters		**Baseline**	**4 Weeks**	**8 Weeks**
1	Height (cm)			
2	Weight (kg)			
3	BMI (kg/m²)			
4	Systolic BP (mmHg)			
5	Diastolic BP (mmHg)			
Biochemical Parameters		**Baseline**	**4 Weeks**	**8 Weeks**
1	Serum Creatinine (mg/dL)			
2	eGFR (mL/min/1.73m²)			
3	Serum Potassium (mmol/L)			
4	Fasting Blood Sugar (mg/dL)			
5	2-hour Postprandial Blood Sugar (mg/dL)			
6	Urine Albumin-Creatinine Ratio (UACR) (mg/g)			

7	Urine R/E – Albumin:			
8	Urine R/E – RBC:			
9	Urine R/E – WBC:			
	Biochemical Parameters	**Baseline**	**4 Weeks**	**8 Weeks**
10	HbA1C (%)		-	-
11	Urine Culture & Sensitivity (if UTI suspected):			
12	Vaginal discharge/penile swab for C/S (if genital mycotic infection suspected)	-		
13	Urine for ketone bodies (if DKA suspected)			
14	Serum bicarbonate (if DKA suspected)			

Adverse Effect			**4 Weeks**	**8 Weeks**
1	Hyperkalemia	1=Yes 2=No		
2	Hypotension	1=Yes 2=No		
3	UTI	1=Yes 2=No		
4	Genital Mycotic Infection	1=Yes 2=No		
5	Hypoglycemia	1=Yes 2=No		
6	Dizziness	1=Yes 2=No		
7	Constipation	1=Yes 2=No		
8	Acute Kidney Injury (AKI)	1=Yes 2=No		
9	Diabetic Ketoacidosis (DKA)	1=Yes 2=No		
10	Fournier's gangrene	1=Yes 2=No		
11	Expired	1=Yes 2=No		
12	Others	1=Yes 2=No		
Outcome		Completed per protol=1, Withdrawn=2, Lost to follow up =3		

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

Consent form

" Effect of dapagliflozin compared to dapagliflozin-finerenone combination on albuminuria in patients with chronic kidney disease and type 2 diabetes: A randomized controlled trial.."

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. Debasis Roy, 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…..

INFORMATION SHEET

for the respondent

ERC Research approval number: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Title of Research: "Effect of dapagliflozin compared to dapagliflozin-finerenone combination on albuminuria in patients with chronic kidney disease and type 2 diabetes: A randomized controlled trial."

Name(s) and affiliation(s) of researcher(s): This research is being conducted by Dr. Debasis Roy, a MD Phase-B Resident, MD (Nephrology) in the Department of Nephrology, Chittagong Medical College, Chattogram, Bangladesh.

Sponsor(s) of Research: This research is self-sponsored

Purpose(s) of Research: The broad aim of this research is to investigates the effect of dapagliflozin-finerenone combination compared to dapagliflozin alone on albuminuria in patients with chronic kidney disease and type 2 diabetes.

Procedure for the Research, what shall be required of each participant and the approximate total number of participants that would be involved in the research: Using a block randomization technique, 88 patients will be grouped by the researcher into two equal groups; 44 patients in Group 1 (that will receive **dapagliflozin-finerenone combination for 8 weeks**) and 44 patients in Group 2 (that will receive **dapagliflozin for 8 weeks**). The urinary albumin excretion, blood pressure, eGFR and adverse events will be studied after 8 weeks.

Expected duration of research and participant(s) involvement: You will be involved in the research till 4 weeks from the enrollment.

Risk(s): The risk or disadvantage to taking part in this study may be the exposure to the some side effects of the drugs including hyperkalemia, hypotension, urinary tract infection, genital mycotic infection, hypoglycemia, dizziness, constipation, acute renal insufficiency, diabetic ketoacidosis and Fournier's gangrene. However, if any adverse events occur, we will manage the conditions as per guideline.

Costs to the participants, if any, of joining the research: You will not require to pay for the drugs, or any related procedure related to the research.

Benefits(s): The finding from this research will help in the management of patients with **chronic kidney disease** and type 2 diabetes in the future.

Confidentiality: All information obtained from participants involved in this research will be coded and personal details will be anonymize.

Voluntariness: Your participant in this research is entirely voluntary. You are free to withdraw your consent at any time during the research. It will not in any way influence the way and manner your condition will be managed.

Alternatives to participation: If you choose not to participate, this will not affect you in any way. You will still have treatment in the routine way and at the usual manner.

Due inducements: No patient will be induced to participate in this research.

Consequences of participants' decision to withdraw from research and procedure for orderly termination of participation: If you decide to withdraw from the research after you have initially consented, it will have no bearing on the modality of managing your conditions at the hospital. The attending physicians will attend to you in the standard way without any discrimination.

Modality of providing treatments and action(s) to be taken in case of injury or adverse event(s): There is no expected serious injury or adverse effects other than the recognized adverse events of the investigating drug. Nevertheless, if any such condition arises it will be managed entirely free of cost.

What happens to research participants and communities when the research is over: The research participants and the community will be informed about the research findings through scientific publications. Any of the research participants willing to obtain any non-confidential information about the research will also be obliged.

Statement about sharing of benefits among researchers and whether this includes or excludes research participants: No direct benefit will be shared among researchers.

Any apparent or potential conflict of interest: No conflict of interest is declared.

Statement of person obtaining informed consent: I have fully explained this research to and have given sufficient information, including the risks and benefits, to guide him to make an informed decision.

DATE:_____/_____/_____

SIGNATURE:_____

NAME: _____

Statement of person giving informed consent: The purpose of this research has been explained to me in details. I consent to taking part know that I will be treated either by **dapagliflozin-finerenone combination or dapagliflozin,** for chronic kidney disease and type 2 diabetes. The risks have been explained to me in details. My participant is entirely voluntary. I understand that am free to withdraw my participant at any time. If I withdraw my participation, it will not alter the standard of my care. All information provided by me will be anonymized and kept in confidence.

DATE:____/____/_____ SIGNATURE/THUMB PRINT: _____

SERIAL NUMBER: _ _ _ _ _ _ _ _ _

WITNESS' SIGNATURE (if applicable): _____

WITNESS' NAME (if applicable): _____

Detailed contact information including contact address, telephone, e-mail and any other contact information of researcher(s), instructional ERC and head of the institution: This research has been approved by the Ethical Review Committee of Chittagong Medical College and they can be contacted at the College Building, Chittagong Medical College. Also, if you have any question about your participation in this research, you can contact the researcher, Name: Dr. Debasis Roy, MD Phase-B Resident, MD (Nephrology) in the Department of Nephrology, Chittagong Medical College, Chattogram, Bangladesh.

Cell No: 01737376811

Email: debasisroy2014@gmail.com

Appendix

Data and Safety Monitoring Board

"Effect of dapagliflozin compared to dapagliflozin-finerenone combination on albuminuria in patients with chronic kidney disease and type 2 diabetes: A randomized controlled trial."

Name of the researcher: This study is being conducted by Dr. Debasis Roy, 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

"Effect of dapagliflozin compared to dapagliflozin-finerenone combination on albuminuria in patients with chronic kidney disease and type 2 diabetes: A randomized controlled trial."

I ..... myself thesis case no..... of Dr. Debasis Roy 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.....