

Proposed Study Title: <div style="background-color: #e6f2ff; padding: 10px; text-align: center;"> The Impact of Using Nicorandil for the Prevention of Doxorubicin-Induced Cardiotoxicity, including Quality of Life and Cost Analysis among Breast Cancer patients: A Randomized Controlled Trial in Egypt </div>	
NCT number: Not applicable yet Date of the protocol approval in the institution: 2/3/2026	
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Background and Rationale:

Doxorubicin (DOX) is an anticancer agent used in chemotherapy to treat haematological and solid cancers (1-3). In breast cancer, DOX is used in many protocols. one of the well-known chemotherapeutic protocols is AC-T (adriamycin, cyclophosphamide, and paclitaxel)(4).The mechanism of DOX cytotoxicity is due to free radical formation, which is associated with DOX cardiotoxic adverse events (5, 6). DOX-induced cardiomyopathy leads to fibrosis of myocardial cells that causes cardiovascular disorders (7). DOX-cardiotoxicity is considered irreversible (type I) cardiotoxicity. (8). Acute toxicity occurs within 2–3 days of DOX administration, whereas early chronic cytotoxicity occurs within 30 days to 1 year from DOX therapy initiation. Late chronic cardiotoxicity appears 6–10 years after the end of DOX (9). Type II is linked to trastuzumab, which can be potentially reversible upon drug discontinuation.

The total cumulative DOX dose must be below 550 mg/m² to prevent doxorubicin cardiotoxicity (10). Echocardiography remains the gold standard for assessing cardiac function primarily by evaluating the left ventricular ejection fraction (LVEF) (11). Besides, Echocardiography could assess the global longitudinal strain (GLS), a measure of the left ventricle's longitudinal shortening, is more sensitive for detecting early myocardial dysfunction that cannot be assessed by LVEF alone. Changes in GLS can indicate subclinical cardiac impairment, which is considered an early warning sign of doxorubicin-induced cardiotoxicity(11).

Biomarkers of cardiotoxicity are a non-invasive method for early detection in patients undergoing doxorubicin therapy (12). These biomarkers enable clinicians to initiate preventive treatment regimens earlier, as they indicate long-term LVEF deterioration (13, 14). Studies have shown that the risk of DOX cardiotoxicity increases at a cumulative dose of 400 mg/m² without other risk factors (8). DOX-induced cardiotoxicity may lead to increased morbidity and mortality (3).

One of the predictive tools is the Heart Failure Association (HFA) and the International Cardio-Oncology Society (ICOS) risk score (HFA-ICOS) for assessing the baseline cardiovascular risk associated with chemotherapy, especially anthracyclines (15). Yet this tool needs further validation studies(16). As a consequence, for most of the patients with DOX-induced cardiotoxicity, their quality of life will be affected. One of the methods used for quality of life assessment is the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC) Core 30 (QLQ-C30) and another one for breast cancer patients (BR-42). A study has shown the deterioration in the psychological and physical state of breast cancer patients on chemotherapy treatment(17).

DOX could affect the calcium (Ca^{2+}) homeostasis in cardiac muscles, one of the important hallmarks of cardiac contractile dysfunction due to DOX (18). Ca^{2+} signalling determines the force of cardiac muscle contraction (19). DOX treatment could increase intracellular Ca^{2+} and lead to left ventricular dysfunction (20). DOX has also been shown to decrease mitochondrial Ca^{2+} storage capacity, leading to Ca^{2+} overload, mitochondrial dysfunction, and cell death (19). In addition, Dox activates the Nuclear factor kappa B (NF- κ B) pathway, leading to the production of pro-inflammatory cytokines and cardiac cell death (19, 21).

Many antioxidant supplements are used to treat DOX-induced cardiotoxicity (22). Dexrazoxane is the only FDA-approved cardioprotective agent for DOX cardiotoxicity (3, 23). Dexrazoxane is an antioxidant agent licensed in Europe for patients with a DOX cumulative dose $> 300 \text{ mg/m}^2$ or who are continuing doxorubicin therapy. Unfortunately, the clinical use of dexrazoxane is limited because it interferes with the antineoplastic activity of DOX (10, 23). Another cause of dexrazoxane limitation in clinical use is the risk of secondary malignancies (24). Although other supplements like omega 3, vitamin E and levocarnitine have shown significant effects in preclinical studies, only a few have been investigated in clinical practice (22, 25, 26). Yet, few studies have targeted the Ca^{2+} imbalance caused by DOX administration.

Nicorandil (NIC), a nicotinamide ester with a nitrate group, is used in several medical conditions in Japan and Europe (27, 28). It is approved for long-term chronic stable angina and is used to treat and protect the ischemic heart. It has also been investigated in conditions like neurological disorders, hepatoprotective activity, gastric ulcers, and pulmonary injuries (27). Nicorandil's (NIC) NIC's cardioprotective effect was caused by selective activation of the mitochondrial ATP-sensitive K^+ channel (mitoK_{ATP}) and nitric oxide (NO) donor activity (27, 29, 30). These will lead to cardiac muscle relaxation and decrease reactive oxygen species and cell death. They also maintain calcium homeostasis and prevent high intracellular calcium levels, which can cause cellular malfunction and apoptosis (27).

Available studies show promising results for NIC in patients with heart failure. Preclinical studies suggested that NIC may also have a protective effect against DOX-induced cardiotoxicity by avoiding mitochondrial dysfunction without affecting the antitumor activity of DOX (28, 30). Further clinical studies are needed to confirm the protective effect of NIC against DOX-induced cardiotoxicity.

Problem statement & Study rationale

Although doxorubicin remains an important component of breast cancer chemotherapy, its clinical use is limited by cardiotoxicity, which may result in subclinical myocardial dysfunction, reduced left ventricular function, heart failure, treatment interruption, and long-term cardiovascular morbidity. Doxorubicin-induced cardiotoxicity is mediated through multiple mechanisms, including oxidative

stress, lipid peroxidation, mitochondrial dysfunction, calcium dysregulation, inflammation, and apoptosis.

Several antioxidant or metabolic supplements, such as vitamin E, L-carnitine, omega-3 fatty acids, and vitamin D, have been investigated for their potential role in reducing doxorubicin-induced cardiotoxicity. However, clinically established cardioprotective options remain limited. Dexrazoxane is an approved cardioprotective agent for anthracycline-related cardiotoxicity, but its use is generally restricted to selected high-risk patients because of cost, availability, regulatory limitations, and historical concerns regarding anticancer efficacy and long-term safety. Therefore, there is a need to explore alternative cardioprotective agents that are clinically feasible, safe, and do not compromise the anticancer effect of doxorubicin.

Nicorandil is a nicotinamide ester with nitrate-like activity and mitochondrial ATP-sensitive potassium channel-opening properties. Preclinical studies suggest that nicorandil may attenuate doxorubicin-induced cardiotoxicity by preserving cardiac function, reducing oxidative injury, maintaining mitochondrial function, and improving echocardiographic parameters. However, clinical evidence on the cardioprotective effect of nicorandil in breast cancer patients receiving doxorubicin remains limited.

In addition to cardiac protection, early identification of patients at risk of doxorubicin-induced cardiotoxicity is clinically important. Although baseline cardiovascular risk stratification tools such as the HFA-ICOS score are recommended in cardio-oncology practice, their predictive performance requires further validation in specific patient populations and local clinical settings. Furthermore, doxorubicin-related cardiotoxicity may impair patients' physical functioning, fatigue, emotional well-being, and overall quality of life. Patient-reported quality-of-life outcomes may therefore provide complementary information to echocardiographic and biomarker-based cardiac assessment.

Study Hypothesis:

Null Hypothesis (H_0): Nicorandil has no significant protective effect on LVEF in breast cancer patients on doxorubicin.

Alternative Hypothesis (H_1): Nicorandil provides a significant protective effect against doxorubicin in breast cancer patients.

Null Hypothesis (H_0): Nicorandil has no significant protective effect on echocardiogram parameters in breast cancer patients on doxorubicin.

Alternative Hypothesis (H_1): Nicorandil provides a significant protective effect on echocardiogram parameters in breast cancer patients on doxorubicin.

Null Hypothesis (H_0): Nicorandil has no significant protective effect on cardiac biomarkers in breast cancer patients on doxorubicin.

Alternative Hypothesis (H_1): Nicorandil provides a significant protective effect on cardiac biomarkers in breast cancer patients on doxorubicin.

Null Hypothesis (H_0): Nicorandil is not significantly safe in breast cancer patients on doxorubicin.

Alternative Hypothesis (H_1): Nicorandil is significantly safe in breast cancer patients on doxorubicin.

Null Hypothesis (H_0): Nicorandil has no significant effect on tumor growth in breast cancer patients on doxorubicin.

Alternative Hypothesis (H_1): Nicorandil has a significant effect on tumor growth in breast cancer patients on doxorubicin.

Null Hypothesis (H_0): Nicorandil has no significant effect on the quality of life of breast cancer patients on doxorubicin.

Alternative Hypothesis (H_1): Nicorandil has a significant effect on the quality of life of breast cancer patients on doxorubicin.

Null Hypothesis (H_0): Nicorandil has no significant effect on the quality of life of breast cancer patients on doxorubicin.

Alternative Hypothesis (H_1): Nicorandil has a significant effect on the quality of life of breast cancer patients on doxorubicin.

Null Hypothesis (H_0): "No-Sexual-Part" Modified EORTC (QLQ-BR42 and QLQ-C30) does not significantly correlate with the actual heart damage found on Echo.

Alternative Hypothesis (H_1): "No-Sexual-Part" Modified EORTC (QLQ-BR42 and QLQ-C30) significantly correlates with the actual heart damage found on Echo.

Null Hypothesis (H_0): "No-Sexual-Part" Modified EORTC cannot replace physician-led risk scores (HFA) in predicting DOX-induced cardiotoxicity.

Alternative Hypothesis (H_1): "No-Sexual-Part" Modified EORTC can replace physician-led risk scores (HFA) in predicting DOX-induced cardiotoxicity.

Null Hypothesis (H_0): Modified HFA-ICOS, when integrated with the EORTC score, will not demonstrate superior diagnostic accuracy and cost utility for predicting subclinical DOX-induced cardiotoxicity compared with standard baseline risk assessment alone.

Alternative Hypothesis (H_1): Modified HFA-ICOS, when integrated with the EORTC score, will demonstrate superior diagnostic accuracy and cost utility for predicting subclinical DOX-induced cardiotoxicity compared with standard baseline risk assessment alone.

Null Hypothesis (H_0): Nicorandil is not cost-effective as a cardioprotective agent against DOX-induced cardiotoxicity.

Alternative Hypothesis (H_1): Nicorandil is cost-effective as a cardioprotective agent against doxorubicin cardiotoxicity.

Null Hypothesis (H_0): Nicorandil does not improve the cost-utility as a cardioprotective agent against DOX-induced cardiotoxicity.

Alternative Hypothesis (H_1): Nicorandil improves the cost-utility as a cardioprotective agent against DOX-induced cardiotoxicity

Objectives

Primary Objectives

1. To evaluate the effect of nicorandil on left ventricular ejection fraction in breast cancer patients receiving doxorubicin.
2. To assess the effect of nicorandil on conventional echocardiographic parameters, including left ventricular diastolic diameter, left ventricular systolic diameter, and fractional shortening.
3. To evaluate the safety of nicorandil based on liver function, renal function, haemodynamic parameters, and clinical signs of gastrointestinal bleeding or ulceration.

Secondary Objectives

1. To determine the effect of nicorandil on global longitudinal strain in breast cancer patients receiving doxorubicin.
2. To assess the effect of nicorandil on cardiac biomarkers, including cardiac troponin and creatine kinase-MB.
3. To evaluate the effect of nicorandil on tumour size among patients receiving neoadjuvant therapy.
4. To assess patients' quality of life using the modified EORTC QLQ-BR42 and QLQ-C30 questionnaires, excluding sexual-function items.

5. To examine the association between modified EORTC quality-of-life scores and echocardiographic evidence of doxorubicin-induced cardiotoxicity.
6. To compare the predictive performance of the modified EORTC quality-of-life scores, the modified HFA-ICOS risk score, and their combined model for detecting subclinical doxorubicin-induced cardiotoxicity.
7. To evaluate the cost-effectiveness and cost-utility of nicorandil as a cardioprotective agent against doxorubicin-induced cardiotoxicity.

List of Correlative Studies:

Year	Research data	Findings
2013	(Ihab T. Abdel-Raheem et.al) in Egypt using rats.	This study shows the negative effect of DOX on body weight and mortality. DOX significantly increased superoxide production, and this effect was inhibited by nicorandil. As well as, Nicorandil pre-treatment reduced elevated LDH and CK activities and improved nitric oxide levels(31).
2013	(Lamiaa A. Ahmed and Shohda A. EL-Maraghy) in Egypt using rats.	Heart function was enhanced by restoring heart rate and aortic blood flow to baseline levels. Nicorandil could preserve energy production and enhance mitochondrial oxygen consumption through the opening of mitoKATP channels. Doxorubicin treatment increased lipid peroxidation, decreased glutathione (GSH) levels, as well as alterations in superoxide dismutase

		<p>(SOD) and catalase activities, which induce oxidative stress in mitochondria.</p> <p>This study showed that doxorubicin treatment led to significant energy impairment by reducing mitochondrial oxidative phosphorylation capacity and decreasing phosphocreatine (PCr) and adenine nucleotide levels.</p> <p>The study showed that doxorubicin's binding to cardiolipin in the inner mitochondrial membrane could compromise mitochondrial function and impair energy production. Nicorandil's administration significantly alleviated these alterations. Nicorandil prevented apoptosis by maintaining caspase-3 activity, in addition to suppressing proapoptotic proteins (cytochrome c, Bax, and caspase-3) and enhancing antiapoptotic protein (Bcl-2) (30).</p>	
2014	(R H Malabade et.al) in India using rats.	<p>This study aims to assess the combination of mandarin oil and nicorandil for cardio protection against Dox-induced cardiotoxicity. The study shows better results with nicorandil alone than with its combination, in reducing serum and heart tissue cardiac marker enzymes (ALT, AST, LDH, and CK-MB). Pre-treatment with nicorandil and mandarin oil resulted in a marked increase in HDL and a decrease in LDL, VLDL, and total cholesterol levels compared with DOX. The combination of nicorandil and mandarin oil has a greater effect on increasing sodium oxide dismutase and glutathione. Both mandarin oil and nicorandil significantly reduce malondialdehyde (MDA) levels by inhibiting DOX-induced lipid peroxidation caused by DOX . The combination therapy shows more significant results on decreasing the QT interval while alone therapy is more significant on decreasing the heart rate(32).</p>	
2017	(Mari C. Asensio-Lo'pez et. al) in Spain using HL1 cellular model.	<p>The results indicated that nicorandil protects HL-1 cardiomyocytes from doxorubicin-induced oxidative stress by enhancing NO production depending in the dose, inhibiting ROS generation by mitkAtp opening, and improving mitochondrial function, through mitochondrial depolarization and a decrease in lipid peroxidation, as indicated by reduced MDA levels (28).</p>	

2021	(Yixuan Wan et.al) in China using rats	The results indicated that the earliest detectable change in heart connection due to DICM was an increase in T2 mapping time, used as an index of myocardial edema, at week 2 in the doxorubicin-treated group. This change was significant when compared to the group treated with both doxorubicin and nicorandil. At week 6, the left ventricular ejection fraction (LVEF) and global peak systolic myocardial strain were reduced in the doxorubicin group. However, these adverse effects were notably less pronounced in the rats that received nicorandil treatment. Histopathological evaluations further supported these findings, showing that nicorandil treatment resulted in less fibrosis, apoptosis, and inflammatory cytokine production in the cardiac tissue(31).	
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Study Methodology

a) Study Design and Data Collection:

- This will be a prospective, open label , parallel, phase 2, two-arm randomized clinical trial. Justification for open-label: No matched placebo; nicorandil has recognizable nitrate-like effects that can unblind; objective endpoints mitigate bias.

- **Study area**

This study will be conducted on females with breast cancer at the National Cancer Institute Hospital in Cairo, Egypt(Single site) .The estimated recruitment follow will depend on the fitted patients within the inclusion and exclusion criteria around 20 patients per week .

b) Technique:

Patients who meet the specified inclusion and exclusion criteria and are eligible for DOX and Nicorandil treatment will be randomly assigned to one of the two groups. Both groups will receive an AC regimen (doxorubicin 60 mg/m² intravenous every 21 days, cyclophosphamide 600 mg/m² intravenous every 21 days for 4 cycles). The total cumulative dose of doxorubicin will be 240 mg/m².

The control group (A):

Besides AC, patients in this group will receive treatment and management as per routine care without nicorandil therapy

The intervention group (B):

Besides AC, other treatment and management as per routine care, patients in this group will receive nicorandil tablets once daily for 6 months,

Doses and duration of Nicorandil:

10 mg twice daily for 6 months. The dose will be started at 5 mg twice a day for 2 days before doxorubicin therapy, then up titrated to 10 mg twice a day to avoid headaches. (27, 33) The dose will be down-titrated to 5 mg twice daily if the patients are intolerant to headache or hypotension.

The control group is going to receive their anticancer protocol. If the left ventricular ejection fraction is below 55 % or develop cardiac symptoms. The chemotherapy protocol will be changed.

Follow up:

Compliance must be monitored by checking empty tablet blisters of NIC before dispensing a refill at each cycle. If patients take more than 80% of the prescribed tablets, they will be considered adherent to the treatment. (34) Patients who will not adhere to the medication will be excluded.

c) Study population

Newly diagnosed breast cancer females at the National Cancer Institute (Cairo, Egypt) who are eligible for the AC treatment protocol.

Subject criteria for both control and intervention groups

A. Inclusion criteria

- 1) 18 years – 65 years
- 2) Female patients with stage (I, II, III) breast cancer.
- 3) Left ventricular ejection fraction (LVEF) $\geq$ 55 % upon breast cancer diagnosis.
- 4) Systolic blood pressure $\geq$ 90 mmHg
- 5) Estimated glomerular filtration rate (eGFR $\geq$ 60 mL/min per 1.73 m²).

B. Exclusion criteria

- 1) Pregnant and lactating mothers.
- 2) Metastatic breast cancer. (stage IV).
- 3) Patients are currently using beta-blockers and phosphodiesterase 5 inhibitors.
- 4) Patients who require chronic use of aspirin or chronic use of corticosteroids ($\geq$ 3 months).
- 5) Patients who are diagnosed with heart failure, myocardial infarction, stable angina, cardiogenic shock, hypovolemia, or previous coronary revascularization.
- 6) Previously treated with anthracyclines.
- 7) Previous gastrointestinal bleeding, ulcer, or perforation.

- 8) Severe hepatic impairment (ALT, AST $\geq$ 5 Upper limit normal), or diagnosed with clinical evidence of hepatic ascites, encephalopathy, variceal bleeding, decompensated cirrhosis, and acute hepatitis.

Data Collection :

Baseline	At the 3 rd month of the treatment	At the 6 th month of the treatment	After the data collection	Future work
Demographic data <ul style="list-style-type: none">○ Patient age, weight, and height○ Body mass index (BMI)○ Body surface area (BSA)			1- Cost analysis 2- Assess the modified HFA - ICOS risk score 3- Assess modified EORTC	1-year follow-up. 5 years follow-up.
Clinical assessment <ul style="list-style-type: none">✓ Medication history (chemotherapy, vitamins, drugs, radiotherapy).✓ Medical history and past surgical history.✓ Breast cancer staging .✓ Hormonal receptors status (Estrogen receptor, Progesterone receptor, Human epidermal growth factor receptor 2).✓ Heart failure staging and NYHA classification✓ HFA-ICOS risk score for doxorubicin cardiotoxicity.				
Investigations and Laboratory tests <ul style="list-style-type: none">✓ (Echo): LVEF , LVDD, LVSD , GLS, FS✓ (CK-MB)✓ (c.TN)✓ (ALT, AST)✓ (eGFR)✓ (CBC)<ul style="list-style-type: none">✓ tumor size pre- and post-treatment for neoadjuvant patients.				
The safety screening measure: (CTCAE) Version 5. <ul style="list-style-type: none">✓ Blood pressure and heart rate				

<ul style="list-style-type: none"> ✓ Signs of gastrointestinal bleeding or ulcer ✓ Cardiotoxicity will be classified according to Cancer Therapy-related Cardiac Dysfunction Definition and Grading(CTRCD) . 			
<p>Quality of life assessment: EORTC (QLQ-BR42 and QLQ-C30).</p>			
<p>Sample size (number of participants included): 146 breast cancer patients will be included.</p> <p>The sample size will be calculated to be 116 patients using G power 3.1.9.4 software with a p-value of 0.05 and a power of 90 % by two independent means t-tests. After calculation, the effect size will be 0.6101909(35). We have to take into account that some patients will need radiotherapy, which affects the cardiac outcome according to EMA (European Medicines Agency) Guideline E9: Statistical Principles for Clinical Trials (36). The inflation factor will be 15 % Based on Whitehead et al. (2016). They discussed that when "covariate adjustment" or stratification is used, a 10–15% increase in sample size protects against "second-order precision loss" (the risk that variance is higher than estimated in the pilot) (37). The sample size will be 133 patients by adding 10% in case of attrition or non-adherent patients. The total sample size will be around 146 patients, which means 73 patients in each group.</p> <p>Statistical analysis:</p> <p>Data will be analyzed using SPSS win (statistical package of social science) version 26. Numerical data will be presented as means, standard deviation, median and ranges as appropriate. While categorical data will be presented as frequencies and percentages. Comparison between two groups of numerical data will be performed using student t-test or non parametric Mann Whitney test as appropriate. While comparison between groups of categorical data will be performed using Chi-Square test or Fisher's exact as appropriate. To measure the strength of association between the normally distributed measurements, Pearson's correlation coefficients will be computed. Spearman's correlation coefficients will be calculated for non-normally distributed numeric variables (r is the correlation coefficient & it ranges from -1 to +1). All tests will be two-sided. Probability (p-value) equal or less than 0.05 will be considered significant.</p> <p>Sampling method and subject recruitment</p> <p>To eliminate major confounding variables associated with radiation-induced myocardial injury, patients will be prospectively stratified into two distinct clinical strata (patients will receive radiotherapy, patients</p>			

will not receive radiotherapy). The permuted block size is 4. That means each 2 get NIC, the other 2 will get the control therapy. Patients will be allocated in a 1:1 ratio to either the Nicorandil intervention arm or the standard control arm using permuted blocks mapping a random integer sequence (1 to 6) to the six mathematically balanced permutations of a four-slot block (AABB, ABAB, ABBA, BAAB, BABA, BBAA). The patients will be allocated in the strata groups using an Excel random generator for randomization. By using an Excel sheet permuted block design. This will ensure the proper allocation of all the factors that may affect the results

Ethical committee approval:

The study is approved by the department counsel at the 2nd of March 2026 .

Ethically approved by 13th Sep 2026

Protection of privacy and confidentiality:

The eligible breast cancer patients will be informed about the study and asked to sign a written informed consent before the trial without any obligation on them to continue if they want to quit the trial at any time. Patient approval or refusal for the study will not affect their right to take the maximum health care. All the patients' data will be secured by the investigator and the physician who is responsible of their medical condition. Only research team members can access the data. Data will be presented as grouped data and will not identify the responders individually. All data of patients will be secured by the investigator. The samples will be stored by the institution's labs until the analysis is done. The data after the analysis is done will be written in an encrypted Excel sheet by the investigator until the end of the study for statistical analysis. The data will be kept for 5 years post the trial according to the good clinical practice regulations.

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CONTOH
ATTACHMENT B

RESEARCH INFORMATION

Research Title: **The Impact of Using Nicorandil for the Prevention of Doxorubicin-Induced Cardiotoxicity, including Quality of Life and Cost Analysis in Breast Cancer Patients: A Randomized Controlled Trial in Egypt**

NCT number: Not applicable yet

Date of the protocol approval in the institution: 2/3/2026

Name of main and co-Researcher

Principle investigator: Noha S Abdelaziz -Phd Candidate- Univesiti Sains Malaysia

Main supervisor: Assoc Prof Dr Sabariah N H -Univesiti Sains Malaysia

Co-supervisor: Ms Nur Hafzan Md Hanafiah lecturer -Univesiti Sains Malaysia

Co-supervisor: **Prof Dr. Ayman A G - National Cancer institute**

INTRODUCTION

You [person under your care / guardian] are invited to take part voluntarily in a research study [interventional research]. This research is about investigating whether adding a heart-protective medication called **Nicorandil** to standard **anticancer** (doxorubicin) can preserve **heart** function, and maintain your overall quality of life during and after treatment.

It is important that you read and understand this research information before agreeing to participate in this study. You will receive a copy of this form to keep for your records if you agree to participate.

Your participation in this study is expected to take **six months** . This study is estimated to include up to **146** participants.

PURPOSE OF THE STUDY

The purpose of this study is to determine **whether taking a heart-protective medication called Nicorandil alongside your standard anticancer (Doxorubicin) can help protect your heart from any drug associated harm , preserve your heart function, maintain your overall quality of life, and be a cost-effective treatment option.**

PARTICIPANTS CRITERIA

The research team members will discussed your eligibility to participate in this study. It is important that you are completely truthful with the staff **including your health history** .

This study will include individuals who are :

1. Females aged between 18 and 65 years old.
2. Newly diagnosed with Stage I, II, or III breast cancer and scheduled to receive Doxorubicin-based chemotherapy (AC regimen).
3. Having normal heart function at diagnosis (Left Ventricular Ejection Fraction $\geq 55\%$). Having adequate blood pressure (systolic blood pressure ≥ 90 mmHg) and healthy kidney function.

This study will not include individuals who are:

1. Pregnant or breastfeeding.
2. Diagnosed with Stage IV (metastatic) breast cancer.
3. Currently taking certain heart or blood pressure medications, such as beta-blockers or phosphodiesterase-5 inhibitors.
4. Taking long-term aspirin or steroid medications (for 3 months or longer).
5. Diagnosed with pre-existing heart conditions (such as heart failure, previous heart attack, angina, or coronary surgery).
6. Previously treated with anthracycline chemotherapy.

7. Having a history of stomach ulcers, gastrointestinal bleeding, or severe liver disease.

STUDY PROCEDURES

if you agree to participate, you will be randomly assigned to one of two groups with an equal (1:1) chance:

1. **Standard Group (Control):** You will receive your planned chemotherapy treatment (AC regimen: Doxorubicin and Cyclophosphamide every 21 days for 4 cycles) along with standard supportive care.
2. **Nicorandil Group (Intervention):** In addition to your standard chemotherapy treatment, you will take Nicorandil tablets daily for 6 months. You will start with a lower dose (5 mg twice daily for 2 days) to help your body adapt, and then increase to the regular dose (10 mg twice daily).

Study Visits and Data Collection Schedule:

- **Baseline Visit (Before Treatment Starts):** You will undergo a routine physical exam, blood pressure check, electrocardiogram (ECG), an echocardiography (ultrasound of the heart), routine blood tests (heart markers, liver and kidney function, complete blood count), and complete a quality-of-life questionnaire (taking approximately 10–15 minutes).
- **3-Month Visit:** You will undergo a repeat echocardiogram, routine blood tests, blood pressure check, and complete the quality-of-life questionnaire. We will also check your empty medicine blister packs to monitor adherence.
- **6-Month Visit (End of Treatment):** You will complete a final set of heart ultrasounds (echocardiogram), blood tests, blood pressure check, and the quality-of-life questionnaire.

RISKS

- **Nicorandil Side Effects:** The most common side effect of Nicorandil is a mild to moderate headache, especially when starting the drug. To reduce this risk, we start at a lower dose and increase it gradually. If headaches or low blood pressure occur, your doctor may reduce your dose. Less common risks include mild dizziness or rare gastrointestinal mouth/stomach ulcers.
- **Chemotherapy Risks:** Doxorubicin chemotherapy carries known risks (such as nausea, hair loss, fatigue, and potential long-term heart strain), which will be managed by your oncology team according to standard medical guidelines.
- **Echocardiogram and Blood Draws:** Blood draws may cause temporary minor discomfort or bruising at the needle site. Echocardiograms are completely safe, non-invasive ultrasound scans.

Please inform the research staff if you encounter any problems or have any important information that might affect your decision to continue participating in this study **REPORTING HEALTH EXPERIENCES**.

REPORTING HEALTH EXPERIENCES (for health research only).

Please contact, at any time, the following researcher if you experience any health problem either directly or indirectly related to this study.

- **Principal Investigator:** Noha Salah Ahmed Abdelaziz
- **Institution:** National Cancer Institute, Cairo University
- **Contact Phone Number:** 00201012305323

PARTICIPATION IN THE STUDY

Your taking part in this study is entirely voluntary. You may refuse to take part in the study or you may stop your participation in the study at anytime, without any penalty or loss of benefits to which you are otherwise entitled.

Your participation may also be terminated by the research staff without your consent if you are found to be unsuitable to continue in the study based on the study protocol. The research staff will inform you if you need to be withdrawn from the study

POSSIBLE BENEFITS

- **Benefit to Individual:** You will receive additional close monitoring of your heart health, including specialized heart ultrasounds (strain imaging) and cardiac blood tests that may detect any subtle heart changes earlier than standard care.
- **Benefit to Community & University:** The findings from this study will help doctors and researchers understand if Nicorandil can be used as an affordable, effective cardioprotective therapy for future cancer patients in Egypt and worldwide.
- **Compensation:** You will not receive any financial compensation for participating in this study. However, all study-related specialized heart investigations (echocardiograms and cardiac biomarkers) and the Nicorandil study medication will be provided free of charge.

QUESTIONS

If you have any question about this study or your rights, please contact;

Noha S Abdelaziz (Principal Investigator)

Universiti Sains Malaysia

Contact No. :00201012305323

CONFIDENTIALITY

Your information will be kept confidential by the researchers and will not be made publicly available unless disclosure is required by law.

Data obtained from this study that does not identify you individually will be published for knowledge purposes.

Your original records may be reviewed by the researcher, the Ethical Review Board for this study, and regulatory authorities for the purpose of verifying the study procedures and/or data. Your information may be held and processed on a computer. Only research team members are authorized to access your information. The data will be disposed of after the study is completed (state the time period). You have the right to refuse the storage and use of your data in the future.

By signing this consent form, you authorize the record review, information storage and data process described above.

SIGNATURES

To be entered into the study, you or a legal representative must sign and date the signature page [ATTACHMENT S or ATTACHMENT G (for genetic sample only) or ATTACHMENT P]

ATTACHMENT S

Participant Information and Consent Form

(Signature Page)

Research Title:

Researcher's Name:

To become a part this study, you or your legal representative must sign this page. By signing this page, I am confirming the following:

- I have read all of the information in this Participant Information and Consent Form including any information regarding the risk in this study and I have had time to think about it.
- All of my questions have been answered to my satisfaction.
- I voluntarily agree to be part of this research study, to follow the study procedures, and to provide necessary information to the research staff, as requested.
- I may freely choose to stop being a part of this study at anytime.
- I have received a copy of this Participant Information and Consent Form to keep for myself.

Participant Name

Participant I.C No

Signature of Participant or Legal Representative

Date (dd/MM/yy)

Name of Individual

Conducting Consent Discussion

Signature of Individual

Date (dd/MM/yy)

Conducting Consent Discussion

Name & Signature of Witness

Date (dd/MM/yy)

Note: i) All participants who are involved in this study will not be covered by insurance.

ATTACHMENT G

Subject Information and Consent Form (IF APPLICABLE)

(Signature Page – Genetic Sample)

Research Title:

Researcher's Name:

To become a part this study, you or your legal representative must sign this page. By signing this page, I am confirming the following:

- I have read all of the information in this Patient Information and Consent Form including any information regarding the risk in this study and I have had time to think about it.
- All of my questions have been answered to my satisfaction.
- I voluntarily agree to be part of this research study, to follow the study procedures, and to provide necessary information to the doctor, nurses, or other staff members, as requested.
- I may freely choose to stop being a part of this study at anytime.
- I have received a copy of this Participant Information and Consent Form to keep for myself.

Participant Name

Participant I.C No.

Signature of Participant or Legal Representative

Date (dd/MM/yy)

Name of Individual

conducting Consent Discussion

Signature of Individual

Date (dd/MM/yy)

Conducting Consent Discussion

Name & Signature of Witness

Date (dd/MM/yy)

- Note:
- i) All participants who are involved in this study will not be covered by insurance.
 - ii) Excess samples from this research will not be used for other reasons and will be destroyed with the consent from the Human Research Ethics Committee, USM.

Participant's Material Publication Consent Form

Signature Page

Research Title:

Researcher's Name:

To take part in this study, you or your legal representative must sign this page.

By signing this page, I confirm the following:

- I understand that my name will not appear on the materials published and there have been efforts to make sure that the privacy of my name is kept confidential although the confidentiality is not completely guaranteed due to unexpected circumstances.
- All the published materials will be shared among the medical practitioners, scientists, academics, researchers, and journalists worldwide.
- The materials will also be used in local publications, book publications and accessed by doctors, scientists, academics, and researchers worldwide
- I hereby agree and allow the materials to be used in other publications required by other publishers with these conditions:
- The materials will not be used as advertisement purposes nor as packaging materials.

- The materials will not be used out of context – i.e.: Sample pictures will not be used in an article which is unrelated subject to the picture.

Participant Name

Participant I.C No.

Participant's Signature Date (dd/MM/yy)

Name and Signature of Individual

Date (dd/MM/yy)

Conducting Consent Discussion

Note: i) All participants who are involved in this study will not be covered by insurance.