ANCILLARY REVIEWS

Which ancillary reviews do I need and when do I need them? Refer to HRP-309 for more information about these ancillary reviews.			
Select yes or no	**Does your study…**	*If yes…*	***Impact on IRB Review***
☐ **Yes** ☒ **No**	Include Gillette resources, staff or locations	*Gillette Scientific review and Gillette Research Administration approval is required. Contact: research@gillettechildrens.com*	**Required prior to IRB submission**
☒ **Yes** ☐ **No**	Involve Epic, or Fairview patients, staff, locations, or resources?	*The Fairview ancillary review will be assigned to your study by IRB staff Contact:* ancillaryreview@Fairview.org	**Approval must be received prior to IRB committee/ designated review.** **Consider seeking approval prior to IRB submission.**
☒ **Yes** ☐ **No**	Include evaluation of drugs, devices, biologics, tobacco, or dietary supplements or data subject to FDA inspection?	*The regulatory ancillary review will be assigned to your study by IRB staff Contact: medreq@umn.edu* *See: https://policy.umn.edu/research/indide*	
☒ **Yes** ☐ **No**	Require Scientific Review? Not sure? See guidance on next page.	*Documentation of scientific merit must be provided. Contact: hrpp@umn.edu*	
☐ **Yes** ☒ **No**	Relate to cancer patients, cancer treatments, cancer screening/prevention, or tobacco?	*Complete the CPRC application process. Contact: ccprc@umn.edu*	
☐ **Yes** ☒ **No**	Include the use of radiation? (x-ray imaging, radiopharmaceuticals, external beam or brachytherapy)	*Complete the AURPC Human Use Application and follow instructions on the form for submission to the AURPC committee. Contact: barmstro@umn.edu*	**Approval from these committees must be received prior to IRB approval;** **These groups each have their own**
☐ **Yes** ☒ **No**	Use the Center for Magnetic Resonance Research (CMRR) as a study location?	*Complete the CMRR pre-IRB ancillary review Contact: ande2445@umn.edu*	
☐ **Yes** ☒ **No**	Include the use of recombinant or synthetic nucleic acids, toxins, or infectious agents?	*Complete the IBC application via eprotocol.umn.edu Contact:*	

☐ **Yes** ☒ **No**	Include the use of human fetal tissue, human embryos, or embryonic stem cells?	*Contact OBAO for submission instructions and guidance*	**application process.**
☒ **Yes** ☐ **No**	Include PHI or are you requesting a HIPAA waiver?	*If yes, HIPCO will conduct a review of this protocol.* *Contact: privacy@umn.edu*	
☐ **Yes** ☒ **No**	Use data from the Information Exchange (IE)?	*The Information Exchange ancillary review will be assigned to your study by IRB staff* *Contact: ics@umn.edu*	**Approval must be received prior to IRB approval.** **These groups do not have a separate application process but additional information from the study team may be required.**
☐ **Yes** ☒ **No**	Use the Biorepository and Laboratory Services to collect tissue for research?	*The BLS ancillary review will be assigned to your study by IRB staff.* *Contact: cdrifka@umn.edu*	
☐ **Yes** ☒ **No**	Have a PI or study team member with a conflict of interest?	*The CoI ancillary review will be assigned to your study by IRB staff* *Contact: becca002@umn.edu*	
☒ **Yes** ☐ **No**	Need to be registered on clinicaltrials.gov?	*If you select "No" in ETHOS, the clinicaltrials.gov ancillary review will be assigned to your study by IRB staff* *Contact: kmmccorm@umn.edu*	
☒ **Yes** ☐ **No**	Require registration in OnCore?	*If you select "No" or "I Don't Know" in ETHOS, the OnCore ancillary review will be assigned to your study by IRB staff* *Contact: oncore@umn.edu*	**Does not affect IRB approval.**

PROTOCOL COVER PAGE

Protocol Title	**Cilostazol for HFpEF**
Principal Investigator/Faculty Advisor	Name: Markus Meyer, MD
	Department: Cardiology
	Telephone Number: 802 922-0656
	Email Address: meye3249@umn.edu
Student Investigator	Name: N/A
	Current Academic Status (Student, Fellow, Resident): N/A
	Department:
	Telephone Number:
	Institutional Email Address:
Scientific Assessment	HRPP facilitated scientific assessment
IND/IDE #	N/A
IND/IDE Holder	N/A
IDS #	5773
Version Number/Date:	1.0 – 11.00.2020

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?

NOTE: Leave this section blank for the initial submission. The revision history should be documented for modifications to approved studies.

Table of Contents

ABBREVIATIONS/DEFINITIONS

Include any abbreviations or definitions for key or technical terms you use in your protocol.

- HFpEF Heart Failure with a preserved ejection fraction
- NTproBNP N-terminal B-type natriuretic protein (heart failure blood marker)

1.0 Objectives

1.1 Purpose:
Determine if cilostazol improves symptoms and NTproBNP levels (heart failure blood marker) in heart failure with preserved ejection fraction (HFpEF) – a prevalent syndrome without evidence-based treatment.

This will be assessed in a prospective 1-month single blinded study with 2 cross-overs (n-of-1 study design with placebo and cilostazol)

1.2 Primary outcome:
1. standardized heart failure questionnaire
(sample provided at the end of the consent document)

1.3 Secondary outcome:
2. NTproBNP

2.0 Background

2.1 Significance of Research Question/Purpose:

Heart failure (HF) is the #1 reason for hospital admissions. About half of the patients with HF have a preserved ejection fraction (HFpEF). There is no evidence-based treatment for HFpEF. We recently reported that beta-blockers increase the risk for HF admissions in HFpEF, in part by their heart rate lowering effects (1-3). On the contrary, we found that elevating the heart rate with pacemakers conveys significant clinical benefits e.g. reduction in heart failure symptoms, lowering filling pressures and an increase in walk distance (4-6). Cilostazol increases the heart rate by about 5-8 beats per minute and has other potentially beneficial HFpEF effects such as peripheral vasodilation, lusiotropic effects (acceleration of relaxation) and dromotropic effects (improved cardiac electrical conduction). By activating proteinkinase A, cilostazol may also phosphorylate titin, which would reduce myocardial stiffness (6).

2.2 Preliminary Data:

Cilostazol is approved for the use in peripheral artery disease and has been used in patients with diastolic dysfunction-induced atrial fibrillation and HFpEF. This results in a symptomatic relief and significant reductions in the heart failure blood marker BNP (7,8). In our own clinical experience, cilostazol reduces HFpEF symptoms and lowers NTproBNP by about 25% to suggest a clinical benefit that is in line with the cilostazol-induced changes in BNP in patients with atrial fibrillation (7,8). No adverse effects were noted in our own HFpEF patients that chronically take cilostazol.

2.3 Existing Literature:

1. Meyer M, LeWinter M Heart Rate and Heart Failure with Preserved Ejection Fraction. Time to Slow β-Blocker Use? Circ Heart Fail. 2019
2. Silverman DN, Plante TB, Infeld M, Callas PW, Juraschek SP, Dougherty GB, Meyer M. Association of β-Blocker Use With Heart Failure Hospitalizations and Cardiovascular Disease Mortality Among Patients With Heart Failure With a Preserved Ejection Fraction: A Secondary Analysis of the TOPCAT Trial. JAMA Netw Open. 2019 Dec 2;2(12):e1916598. doi: 10.1001/jamanetworkopen.2019.16598.
3. Nambiar L, Silverman D, Vanburen P, LeWinter M, Meyer M. Beta-Blocker Cessation in Stable Outpatients With Heart Failure With a Preserved Ejection Fraction. J Card Fail. 2019 Aug 31. pii: S1071-9164(19)30616-5. doi: 10.1016/j.cardfail.2019.08.020. [Epub ahead of print]
4. Wahlberg K, Arnold ME, Lustgarten D, Meyer M. Effects of a Higher Heart Rate on Quality of Life and Functional Capacity in Patients with Left Ventricular Diastolic Dysfunction American Journal of Cardiology 2019
5. Silverman DN, Rambod M, Lustgarten DL, Lobel R, LeWinter MM, Meyer M. Heart Rate-Induced Myocardial Ca2+ Retention and Left Ventricular Volume Loss in Patients With Heart Failure With Preserved Ejection Fraction. J Am Heart Assoc. 2020 Sep;9(17):e017215. doi: 10.1161/JAHA.120.017215. Epub 2020 Aug 28. PMID: 32856526.
6. Zile MR, Baicu CF, Ikonomidis JS, Stroud RE, Nietert PJ, Bradshaw AD, Slater R, Palmer BM, Van Buren P, Meyer M, Redfield MM, Bull DA, Granzier HL, LeWinter MM. Myocardial stiffness in patients with heart failure and a preserved ejection fraction: contributions of collagen and titin. Circulation. 2015 Apr 7;131(14):1247-59. doi: 10.1161/CIRCULATIONAHA.114.013215. Epub 2015 Jan 30.
7. Kishida M, Watanabe K, Tsuruoka T. Effects of cilostazol in patients with bradycardiac atrial fibrillation. J Cardiol. 2001 Jan;37(1):27-33.
8. Atarashi H, Endoh Y, Saitoh H, Kishida H, Hayakawa H. Chronotropic effects of cilostazol, a new antithrombotic agent, in patients with bradyarrhythmias. J Cardiovasc Pharmacol. 1998 Apr;31(4):534-9.
9. Nanayakkara S, Byrne M, Mak V, Carter K, Dean E, Kaye DM. Extended-release oral milrinone for the treatment of heart failure with preserved ejection fraction. J Am Heart Assoc. 2020; 9:e015026. DOI: 10.1161/JAHA.119.015026.
10. Burkhoff D, Borlaug BA, Shah SJ, et al. Levosimendan Improves Hemodynamics and Exercise Tolerance in PH-HFpEF: Results of the Randomized Placebo-Controlled HELP Trial. JACC Heart Fail 2021 doi: 10.1016/j.jchf.2021.01.015 [published Online First: 2021/04/03

3.0 Study Endpoints/Events/Outcomes

Endpoint/Event/Outcomes:
1. standardized heart failure questionnaire
2. NTproBNP

4.0 Study Intervention(s)

4.1 Description:

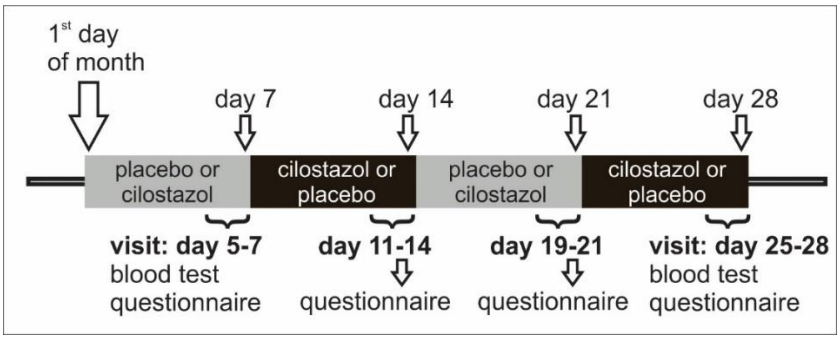
We propose a n-of-1 study design using the standard dose cilostazol formulation of 100mg twice a day approved in peripheral vascular disease. The patients will be blinded and serve as their own controls with two crossovers (cilostazol – placebo – cilostazol - placebo). This exploratory study is neither designed nor powered to seek a change in

the drug approval and thereby does not require an FDA investigational new drug (IND) application (see section 4.1). The study aims to minimize in-person visits during the ongoing COVID-19 pandemic.

Study Flow:

1. Screening of clinic patients
2. Informed Consent
3. Study drugs distribution by the pharmacy
4. Study start (1st of month)
5. Interventions (see below)
6. Study end (end of month)

Cilostazol 100mg BID (white) versus Placebo BID
(colored or different shape – to confirm adherence)



The cilostazol and placebo pills are in a preloaded pill-organizer box (see below).
- study start at first day of the month (to facilitate adherence)
- two in person study visits on **day 5-7** and **day 25-28** for blood draw and vital signs
- four scheduled phone calls (days: **7, 14, 21 and 28**) : heart failure questionnaires

4.2 Cilostazol Adverse Effects

For cilostazol's relationship to milrinone (PDE3 inhibitor inotrope) a theoretical concern was raised that cilostazol may increase the risk for sudden death or may worsen congestive heart failure with reduced ejection fraction as detailed below: However, in the studies that led to FDA approval in 1999, cilostazol was determined to have a good safety profile. In a randomized study of 1,439 patients that included recovered ejection fraction heart failure patients, the 36 months cumulative mortality rates were 6.8% in the placebo group and 5.6% in the cilostazol group, a non-significant difference. Despite an absence of adverse outcomes, a precautionary safety warning for patients with reduced ejection fraction congestive heart failure was included in the drug label. Nevertheless,

cilostazol is sometime used as a modestly effective inotrope (agent that increases cardiac contractility) in end-stage heart failure with a reduced ejection fraction.

The most common cilostazol adverse effect is a headache (+20% over placebo), abdominal symptoms and diarrhea (+12% over placebo) and palpitations (+9% over placebo).

The aforementioned milrinone, which is more potent than cilostazol, was recently reported to improve HFpEF. In the US, milrinone is only approved as an intravenous agent (9). Similarly, levosimendan was recently reported to provide hemodynamic and symptomatic benefits (10).

The package insert includes the risk of left ventricular outflow tract obstruction, any type of heart failure, bleeding dyscrasias, blood dyscrasias and drug interactions

Source: https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/020863s021lbl.pdf

Detail the FDA exemption:

After reviewing the information contained in your submission, we have concluded that your study, "Cilostazol for HFpEF," meets all of the requirements for exemption from the investigational new drug (IND) regulations and, therefore, an IND is not required to conduct your investigation.

The IND regulations [21 CFR 312.2(b)] state that the clinical investigation of a drug product, including a biological product, that is lawfully marketed in the United States, is exempt from the requirements for an IND if all of the following apply:

(1) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use, nor intended to be used to support any other significant change in the labeling for the drug.

(2) The investigation is not intended to support a significant change in the advertising for a prescription drug product.

(3) The investigation does not involve a change in route of administration, dosage

level, or patient population, or other factor that significantly increases the risks (or decreases the acceptability of risks) associated with use of the drug product.

(4) The investigation is conducted in compliance with the requirements for institutional review (21 CFR 56) and informed consent (21 CFR 50).

(5) The investigation is conducted in compliance with the requirements of 21 CFR 312.7, i.e., the drug may not be represented as safe or effective, nor may it be commercially distributed, for the purposes for which it is under investigation.

4.3 Drug storage/ handling and administration:

Cilostazol and placebos will be provided by the Fairview IDS pharmacy and preloaded into the 1 month pill box and given or shipped to the patient after consent is obtained.

The pill box has 31 removable medication vials for each day of the month to simplify the administration schedule and increase adherence. The study always starts at the first day of a month.

4.4 Biosafety: N/A

4.5 Stem Cells: N/A

4.6 Fetal Tissue: N/A

5.0 Procedures Involved

5.1 Study Design: prospective single blind placebo controlled n=1 study with 2 cross-overs

5.2 Study Procedures:

- NTproBNP on cilostazol and on placebo (see flow diagram)
  day 5 to 7 (5mL's) and day 25 to 28 (5 mL's) at any Fairview Lab site.
- Kansas City Heart Failure Questionnaire (KCCQ-12)
  will be administered by PI phone call day 7, 14, 21 and 28
- Baseline patient characteristics collected from Fairview EPIC

5.3 Study Duration: 1 month

- The duration anticipated to complete all study procedures, including any long-term follow-up, and data analysis: 12 months

5.4 Use of radiation: N/A

5.5 Use of Center for Magnetic Resonance Research: N/A

6.0 Data and Specimen Banking

6.1 Storage and Access: The primary data collected and stored a password protected UMN PCs as outlined later. In addition the data file will be encrypted and password protected. All computer equipment is in a locked office of the PI at the UMN. Data exported for analysis will only be shared as a de-identified file. The primary identifying data file will be deleted after publication.

6.2 Data:
baseline clinical patient characteristics e.g. age, gender, medications.

dates of study and results

6.3 Release/Sharing: No directly identifying PHI will be released outside the University of Minnesota.

7.0 Sharing of Results with Participants

7.1 Patient will be informed of their personal results: benefit – no benefit.
If requested by the participant the treating provider will be contacted to discuss the potential benefits of a cilostazol prescription.

7.2 Sharing of genetic testing: N/A

8.0 Study Population

Patients with HFpEF are typically >55y/o with an equal gender distribution

Inclusion Criteria:
>18 yrs
LVEF ≥ 50% (on last assessment, <2 years)
Diagnosis of HFpEF **or** Shortness of breath **and** NYHA Class ≥ 2 **and** one of the following:

1. pulmonary edema on chest imaging **or** documented on exam **or** on loop diuretics
2. NTproBNP >400 ng/ml in the last 24 months
3. HFpEF>50% hospitalization in the last 3 years
4. Qualitative echo: > mild diastolic dysfunction on echo report **and** > mild left ventricular hypertrophy **and** left atrial dilation or quantitative echo: left ventricular hypertrophy [men ≥115 g/m², women ≥95 g/m² or relative wall thickness >0.42 or any LV wall thickness >1.2cm **and** has LA dilation (>28ml/m^2)

Exclusion Criteria:
<18yo
resting heart rate >100/min (assessed by pulse or ECG recorded in EPIC)
patients with LVEF <50% and advanced end-stage heart failure (NYHA 3 and 4)
symptomatic COPD on home O2
uncontrolled severe HTN as defined by BP >160/100 mmHg on two checks ≥15 minutes apart
patients with life expectancy <6 months
end-stage liver cirrhosis
more than moderate valve disease
infiltrative myocardial disease (e.g. amyloidosis) or constrictive pericarditis or myocarditis
patients unable to participate in follow up
patients without baseline LVEF data > 2 years
pregnant patients or patients without reliable contraceptive agent (intra-uterine device, birth control implant, compliance with contraception injections or contraception pills) for the duration of study participation)
left ventricular outflow tract obstruction

bleeding dyscrasias, blood dyscrasias
Patients that take: ketoconazole, itraconazole, fluconazole, miconazole, fluvoxamine, fluoxetine, nefazodone, sertraline, erythromycin, clarithromycin or azithromycin

Screening:
Individuals will be screened or assessed for eligibility during a hospital admission at the UMN Medical Center or in the UMP cardiology outpatient clinics.

9.0 Vulnerable Populations

9.1 Vulnerable Populations:

Population / Group	Identify whether any of the following populations will be targeted, included (not necessarily targeted) or excluded from participation in the study.
Children	Excluded from Participation
Pregnant women/fetuses/neonates	Excluded from Participation
Prisoners	Excluded from Participation
Adults lacking capacity to consent and/or adults with diminished capacity to consent, including, but not limited to, those with acute medical conditions, psychiatric disorders, neurologic disorders, developmental disorders, and behavioral disorders	Excluded from Participation
Non-English speakers	Excluded from Participation
Those unable to read (illiterate)	Included/Allowed to Participate
Employees of the researcher	Excluded from Participation

Students of the researcher	Excluded from Participation
Undervalued or disenfranchised social group	Included/Allowed to Participate
Active members of the military (service members), DoD personnel (including civilian employees)	Included/Allowed to Participate
Individual or group that is approached for participation in research during a stressful situation such as emergency room setting, childbirth (labor), etc.	Excluded from Participation
Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare.	Included/Allowed to Participate
Individual or group with a serious health condition for which there are no satisfactory standard treatments.	Included/Allowed to Participate
Individual or group with a fear of negative consequences for not participating in the research (e.g. institutionalization, deportation, disclosure of stigmatizing behavior).	Excluded from Participation
Any other circumstance/dynamic that could increase vulnerability to coercion or exploitation that might influence consent to research or decision to continue in research.	Excluded from Participation

9.2 Additional Safeguards:

Individuals who are ethnic minorities would not be excluded from this study if they were so inclined to participate. Subjects would be taken through the consent process as per usual if subject is an ethnic minority who is English speaking.

Individuals who are illiterate, would go through the consent as per usual; a witness would sign the consent form, documenting the consent process.

Undervalued or disenfranchised social group (transgender, LGBTQIA+ etc, person of color, etc.) would not be targeted but could be incidentally included if they met criteria and wanted to participate.

Individual or group that is disadvantaged in the distribution of social goods and services such as income, housing, or healthcare are not targeted but could be included. No compensation is provided for participating in this study; thus, subjects from these groups would not feel coerced to participate in order to obtain monetary compensation.

A subject might incidentally be a person with a military background, active or inactive duty. We do not see them in a setting where rank could operate to coerce them into participating.

Risks are minimized through compliance with the study protocol, adherence to the guidelines for selection of subjects, close monitoring of the subject status during the study and follow-up procedures. The sponsor provides training for research staff on this study protocol. This training, extensive knowledge of the protocol along with investigator and research staff experience aid in minimizing risks to subjects.

10.0 Local Number of Participants

10.1 Local Number of Participants to be Consented: 25

11.0 Local Recruitment Methods

11.1 Recruitment Process: Potential patients determined to be possible candidates will be approached in the clinic and/or Hospital. The environment will be conducive to discussion as the patient will be seen privately in a clinic exam room, or in a private exam room. Distractions are kept to a minimum. The visit will occur in a relaxed and open atmosphere conducive for private conversation.

Subjects will be given time to think over whether or not they want to participate in the study. Subjects are free to discuss their options with their primary care or physician and their family members before making their decision.

11.2 Identification of Potential Participants: Potential subjects will be recruited based on information contained in private/protected records (medical records, student records). This also includes subjects who will be recruited from the PI or Co-I's patient population. The PI and Co-Investigators have legitimate access to records per their employment with UMP heart and Fairview hospitals/clinics. Research staff checks for opt-outs and does not review records if the patient has opted out.

Research team members have legitimate access to records by virtue of their employment. Study team members, such as coordinators, are allocated this authority per the Delegation of Authority log. Please note, all involved research staff member have undergone required PHI and Human Subjects training for the

UMN, MHEALTH and Fairview in order to safely, correctly and legitimately access medical records.

Initial contact with potential participants would be made by the treating cardiology providers followed by PI or Co-investigators. A physician or care provider in the cardiology clinic or on the cardiology service will briefly tell the patient about the study and ask if they would like to discuss it further with a member of the research staff (one of the investigators or coordinators). If the patient agrees, a member of the study staff will meet with the patient and discuss the study in more detail.

Potential subjects will come from the UMP Cardiology Clinic/Cardiology Inpatient/Outpatient service where the cardiology provider practice, PI and Co-Investigators clinically manage these patients.

Private/protected records will include MEDICAL records. Research staff will ensure the patient has not opted out of research on the Consent for Treatment and Registration form.

11.3 Recruitment Materials: N/A

11.4 Payment: N/A

12.0 Withdrawal of Participants

12.1 Withdrawal Circumstances:

Patients can withdraw at any time.

Patient can be withdrawn without consent by the PI and key personnel for unexpected adverse events (AEs) or unanticipated problem (UAPs) that could be study related. This would be discussed with Cindy Martin MD, director of heart failure, and reported to the IRB within 48h.

12.2 Withdrawal Procedures:
No continued data collection after withdrawal

12.3 Termination Procedures:
The data will be used for AE and UAP reporting to the IRB and in a publication

13.0 Risks to Participants

13.1 Foreseeable Risks:
Headaches 34% (+20% over placebo)
Palpitations 10% (+9% over placebo)
Diarrhea 19% (+12% over placebo)

Additional Risks:
left ventricular outflow tract obstruction, any type of heart failure, bleeding

dyscrasias, blood dyscrasias and drug interactions.

13.2 Reproduction Risks:
minimal, HFpEF is a disease outside the typical reproductive ages

13.3 Risks to Others:
N/A

14.0 Potential Benefits to Participants

14.1 Potential Benefits:
moderate chance (>30%) at improving heart failure symptoms within 48h after first dose of cilostazol

15.0 Statistical Considerations

15.1 Data Analysis Plan:
Primary outcomes

KCCQ heart failure questionnaire: paired parametric test (t-test) of placebo average composite score and the cilostazol average composite score.

NTproBNP: Relative changes in NTproBNP level (placebo versus cilostazol) will be compared by paired parametric testing (t-test).

15.2 Power Analysis:
In a recent large HFpEF clinical trial of sacubitril/valsartan the baseline KCCQ score was 71 ± 19. A sample size of 18 would provide us with 80% power to detect a 25% relative difference using a 2-sided test. We propose a sample size of 25 participants to ascertain 18 or greater completed studies. In a recently completed pacemaker study that leads to a similar increase in heart rate we found a beneficial outcome in a heart failure questionnaire in n=22 participants (see reference #4, Wahlberg et al.).

15.3 Statistical Analysis:

Linear mixed-effect models determine the effect of cilostazol on the primary outcome, accounting for inter-patient differences and treatment assignment and sequences. For the primary endpoint, the KCCQ total score at the end of each week (week 1 to 4) is the dependent variable, while the treatment (cilostazol versus placebo) is the independent variable. Patient identifier and treatment sequence (binary variable marking the start of the treatment with placebo or cilostazol) are entered as random effects. The same approach was taken to assess the effect of cilostazol on NT-proBNP levels, after log-transforming NT-proBNP values given their skewed distribution. To determine the

treatment effect paired analyses of subsequent treatment periods will be performed (Wilcoxon test) to match weeks and the days within the treatment period.

15.4 Data Integrity:

The de-identified data will be available to all key personnel to yield a fully transparent data analysis.

16.0 Health Information and Privacy Compliance

16.1 Select which of the following is applicable to your research:

☐ My research does not require access to individual health information and therefore assert HIPAA does not apply.

☒ I am requesting that all research participants sign a HIPCO approved HIPAA Disclosure Authorization to participate in the research (combined consent and HIPAA Authorization).

☐ I am requesting the IRB to approve a Waiver or an alteration of research participant authorization to participate in the research.

Appropriate Use for Research:

☐ An external IRB (e.g. Advarra) is reviewing and we are requesting use of the authorization language embedded in the template consent form in lieu of the U of M stand-alone HIPAA Authorization. Note: External IRB must be serving as the privacy board for this option.

16.2 Identify the source of Private Health Information you will be using for your research (Check all that apply)

☐ I will use the Informatics Consulting Services (ICS) available through CTSI (also referred to as the University's Information Exchange (IE) or data shelter) to pull records for me

☒ I will collect information directly from research participants.

☐ I will use University services to access and retrieve records from the Bone Marrow Transplant (BMPT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) database.

☒ I will pull records directly from EPIC.

☐ I will retrieve record directly from axiUm / MiPACS

☐ I will receive data from the Center for Medicare/Medicaid Services

☐ I will receive a limited data set from another institution

☐ Other. Describe:

16.3 Explain how you will ensure that only records of patients who have agreed to have their information used for research will be reviewed.

patients who do not agree to have their PHI assessed cannot be enrolled.

16.4 Approximate number of records required for review: 25

16.5 Please describe how you will communicate with research participants during the course of this research. Check all applicable boxes

☐ This research involves record review only. There will be no communication with research participants.

☒ Communication with research participants will take place in the course of treatment, through MyChart, or other similar forms of communication used with patients receiving treatment.

☐ Communication with research participants will take place outside of treatment settings. If this box is selected, please describe the type of communication and how it will be received by participants.

16.6 Explain how the research team has legitimate access to patients/potential participants:

Subjects will have signed a consent including a HIPAA authorization. Patients are from cardiology group where PI and Co-Investigators have legitimate access to these records.

16.7 Location(s) of storage, sharing and analysis of research data, including any links to research data (check all that apply).

☐ In the data shelter of the Information Exchange (IE)

☐ Store ☐ Analyze ☐ Share

☐ In the Bone Marrow Transplant (BMT) database, also known as the HSCT (Hematopoietic Stem Cell Transplant) Database

☐ Store ☐ Analyze ☐ Share

☐ In REDCap (recap.ahc.umn.edu)

☐ Store ☐ Analyze ☐ Share

☐ In Qualtrics (qualtrics.umn.edu)

☐ Store ☐ Analyze ☐ Share

☒ In OnCore (oncore.umn.edu)

☒ Store ☐ Analyze ☒ Share

☒ In the University's Box Secure Storage (box.umn.edu)

☒ Store ☒ Analyze ☒ Share

☐ In an AHC-IS supported server. Provide folder path, location of server and IT Support Contact:

The path should be in the form of "\\vp.ahc.umn.edu\vp\Research\Study0004" HIPCO requires this information to verify the data are in a properly encrypted server.

☐ Store ☐ Analyze ☐ Share

☐ In an AHC-IS supported desktop or laptop.

Provide UMN device numbers of all devices:
PI #20191597 = password protected PC in locked office PC (PI)
encrypted Excel file

☒ Store ☒ Analyze ☐ Share

☐ Other. Describe: N/A

Indicate if data will be collected, downloaded, accessed, shared or stored using a server, desktop, laptop, external drive or mobile device (including a tablet computer such as an iPad or a smartform (iPhone or Android devices) that you have not already identified in the preceding questions

☐I will use a server not previously listed to collect/download research data

☐I will use a desktop or laptop not previously listed

☐I will use an external hard drive or USB drive ("flash" or "thumb" drives) not previously listed

☐I will use a mobile device such as an tablet or smartphone not previously listed

16.8 Consultants. Vendors. Third Parties. N/A

16.9 Links to identifiable data: OnCore is the CTMS used to link patients to their study IDs. Information will be destroyed after the completion of the study in compliance with the University of Minnesota's documentation destruction policy (https://policy.umn.edu/operations/recordretention-proc02) and HIPAA law.

16.10 Sharing of Data with Research Team Members.
UMN BOX and de-identified data via e-mail

16.11 Storage and Disposal of Paper Documents: The information will be destroyed in accordance with the University of Minnesota's documentation destruction policy (https://policy.umn.edu/operations/recordretention-proc02). The department of Cardiology utilizes established contracts with shredding vendors.

17.0 Confidentiality

17.1 Data Security: De-identified data will be stored in UMN Box. Box Secure Storage is a secure environment delivered by the Center of Excellence for HIPAA Data intended for storing, sharing and accessing sensitive and private-highly restricted files.

Data and samples shared outside the institution: N/A

The consent documents and other documents may be in physical files housed in the PI's secured office. Subjects will be assigned a unique code, which will be included on the associated study data. Only trained members of the research team affiliated with this study will have access to the study information

18.0 Provisions to Monitor the Data to Ensure the Safety of Participants

18.1 Data Integrity Monitoring. Describe the following:

- The PI will personally oversee the progress of the study and to ensure that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures, and applicable regulatory requirements. Maintenance of, and the assurance of, data accuracy and consistency over its entire life-cycle will be monitored by the principle investigator and Dr. Tamas Alexy. NTproBNP and heart failure scores data integrity will be assessed and verified by both investigators.
- CTSI monitoring service will be utilized to provide regular monitoring visits every 6 month or if there is any concern that data integrity is compromised to assure that the study is conducted, recorded, and reported in compliance with Good Clinical Practice. Monitoring is provided at no cost to PIs.

18.2 Data Safety Monitoring.
There is no formal DSMB. AEs and UOPs will be reported to the clinical director of heart failure Dr. Cindy Martin MD. If she recommends a change in protocol this will be directly communicated to the IRB and enrollment will be halted until the changes are approved.

The data will be continuously monitored by the PI and shared in a de-identified file amongst key personnel.

19.0 Provisions to Protect the Privacy Interests of Participants

19.1 Protecting Privacy:

Only affiliated research team member will interact or obtain personal or sensitive information from study subjects.

We do anticipate any of the standard inquiries would make subjects feel uncomfortable; however, subjects do not have to answer questions that might make them feel uncomfortable.

19.2 Access to Participants*:* Subjects will have signed the consent form including HIPAA allowing this access.

20.0 Compensation for Research-Related Injury

20.1 Compensation for Research-Related Injury: We will use the following UMN HRPP template language:

"In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to you or your insurance company. If you think that you have suffered a research related injury let the study physicians know right away."

20.2 Contract Language: N/A

21.0 Consent Process

21.1 Consent Process (when consent will be obtained): The consent process could take place: University of Minnesota Medical Center (UMMC), Clinics and Surgery Center (CSC) and Lillehei Clinical Research Unit (LCRU).

We will allow patients as much time as possible to consider participation in the study. A physician or care provider in the cardiology clinic or on the cardiology service will briefly tell the patient about the study and ask if they would like to discuss it further with a member of the research staff. If the patient agrees, a member of the study staff will meet with the patient and discuss the study in more detail. Potential subjects will come from the UMP Cardiology Clinic/Cardiology Inpatient/Outpatient service where PI and Co-Investigators clinically manage these patients.

Trained and affiliated members of the research team will determined that a potential participant understands the information during the consent process and discussion. Continued consent is accessed at each follow-up visit to ensure subject understanding and continued willingness to participate.

Documentation is comprised of a note in the subject file. The free text note outlines the consent process and discussion; any questions that arose and how the research team addressed those questions.

21.2 Waiver or Alteration of Consent Process (when consent will not be obtained): N/A

21.3 Waiver of Written/Signed Documentation of Consent (when written/signed consent will not be obtained): N/A

21.4 Non-English Speaking Participants: N/A

21.5 Participants Who Are Not Yet Adults (infants, children, teenagers under 18 years of age): N/A

21.6 Cognitively Impaired Adults, or adults with fluctuating or diminished capacity to consent: N/A

21.7 Adults Unable to Consent: N/A

- Permission: N/A
- Assent: N/A
- Dissent: N/A

22.0 Setting

22.1 Research Sites: This information is already provided above in section 11 and 25 of this form; location information is provided in the ETHOS SmartForm.

22.2 International Research: N/A

23.0 Multi-Site Research

N/A

24.0 Coordinating Center Research

N/A

25.0 Resources Available

25.1 Resources Available:

- Sample size is addressed above in section 15 above.
- We will take as much time is required to safety and appropriately conduct the study in compliance with the approved B&I protocol.
- University of Minnesota Medical Center (UMMC), Clinics and Surgery Center (CSC), Fairview outpatient laboratories (any Fairview location), Lillehei Clinical Research Unit (LCRU)
- Affiliated research team is comprised of doctors and nurses with extensive clinical and research experience.
- Everyone obtaining consent has undergone IRB required research training. The PI and Co-PI are established researchers and clinicians with many years of experience in research. The study coordinators and research staff involved are experienced personnel who understand the tenets of good clinical practices.

26.0 References

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