Weill Cornell Medicine NewYork-Presbyterian

Heart Failure with Preserved Ejection Fraction (HFpEF) and Cardiac Amyloidosis Program

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Weill Cornell Medicine | NewYork-Presbyterian

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Pilot Deprescribing N-of-1 Trials for Beta-blockers in HFpEF

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Funding Source(s):	New York Community Trust National Institute on Aging
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Statement of Compliance

(1) [The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from subjects who provided consent, using a previously approved consent form.]

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM.

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Institution Name

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Principal Investigator's Name **Principal Investigator's Signature** **Date**

List of Abbreviations

6MWT	Six – Minute Walk Test
ADL	Activities of Daily Living
ADWE	Adverse Drug Withdrawal Risk
AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
CPET	Cardiopulmonary Exercise Test
CTCAE	Common Terminology Criteria for Adverse Events
CTSC	Clinical Translational Science Center
DM	Dose Modification
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
ECG	Electrocardiogram
EQ5D-VAS	EuroQol Visual Analogue Scale
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HF	Heart Failure
HFpEF	Heart Failure with Preserved Ejection Fraction
HFrEF	Heart Failure with Reduced Ejection Fraction
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HUD	Humanitarian Use Device
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
KCCQ-12	Kansas City Cardiomyopathy Questionnaire 12
PHI	Protected Health Information
PI	Principal Investigator
PRO	Patient Reported Outcomes
PROMIS-SF6A	Patient Reported Outcomes Measurement Information System Short Form
PROMIS-29	Patient Reported Outcomes Measurement Information System 29
RCT	Randomized Clinical Trial
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SPPB	Short Physical Performance Battery
SOA	Schedule of Assessments
SUSAR	Suspected Unexpected Serious Adverse Reaction
UIRTSO	Unanticipated Problem Involving Risks to Subjects or Others
WCM	Weill Cornell Medicine

1. Protocol Summary

Full Title:	*Pilot Deprescribing N-of-1 Trials for Beta-blockers in HFpEF*
Short Title:	*N-of-1 for BB in HFpEF*
Clinical Phase:	NIH Stage 1 of Behavioral Intervention Development
Principal Investigator:	Parag Goyal, MD, MSc
Study Description:	We will determine whether N-of-1 trials, as a pragmatic, patient-centered approach to medication optimization that can overcome key barriers of deprescribing, can lead to increased subject confidence regarding the decision to continue or discontinue beta-blockers in older adults with Heart Failure with Preserved Ejection Fraction (HFpEF).
Sample Size:	N=16
Enrollment:	This study will enroll 16 subjects.
Study Population:	Subjects will be recruited from the HFpEF Program, as well as from the Cardiology, Heart Failure, Geriatrics and/or Internal Medicine clinics at Weill Cornell Medicine.
Enrollment Period:	30 Months
Study Design:	This is an unblinded NIH Stage I of Behavioral Intervention Development trial, using a Crossover intervention model. We will enroll 16 subjects and we will conduct four rounds of N-of-1 trials with four subjects each. We will use a two-arm crossover titration/reversal design (On [A] vs. Off [B]) with up to 4 periods. Subjects will be randomized to either ABAB or BABA (see Figure 1 below). Each period will last up to 6 weeks, allowing for sufficient time for up-titration and onset of drug action, and down-titration and washout. Each subject will have the option to participate in less (2-3) or more periods (5-6) depending on whether they need additional information to make an informed decision about continuing or discontinuing their beta-blocker at the end of this trial. The intervention drug will be beta-blockers, previously prescribed to the subjects by their physician. We have developed a titration algorithm, where we will reduce the dose of each beta-blocker by 50% every week.
Description of Sites/ Facilities Enrolling Subjects:	Enrollment will only be at Weill Cornell Medicine.
Study Duration:	Estimated Primary Completion Date of December 2022
Subject Duration:	1 Year
Study Agent/Device Name	Not applicable

Intervention Description: The intervention is a two-arm crossover withdrawal/reversal design (On [A] vs. Off [B]) with up to 4 periods, each period lasting up to 6 weeks. During the On period (A), subjects will be on their beta-blocker. During the Off period (B), their beta-blockers will be down-titrated and subsequently discontinued; we will decrease the dose of beta-blocker by 50% every week regardless of which beta-blocker they are on, similar to an algorithm used in a prior deprescribing trial. Subjects will be randomized to either ABAB or BABA (see Figure 1 below).

Subjects may be on any of the following beta-blockers:

- Atenolol
- Betaxolol
- Bisoprolol
- Metoprolol
- Metoprolol Succinate
- Metoprolol Tartrate
- Penbutolol
- Nebivolol
- Propranolol
- Acebutolol
- Pindolol
- Carvedilol
- Labetalol
- Nadolol
- Sotalol
- Nadolol

Co-Primary Objectives: To determine the features of a feasible and pragmatic protocol for deprescribing N-of-1 trials in patients with Heart Failure with Preserved Ejection Fraction.
Funded by National Institute on Aging

To compare physical activity between the On and Off phase via:
- Step Count collected via Garmin wearable device

Funded by the New York Community Trust

To compare exercise capacity between the On and Off phase via:
- Peak oxygen consumption (VO2) Cardiopulmonary Exercise Test

Funded by the New York Community Trust

To compare lower extremity function between the On and Off phase via:
- Short physical performance battery (lower extremity function)

Funded by the New York Community Trust

Secondary Objective: To compare Patient Reported Outcomes between the On and Off phase via:
- Kansas City Cardiomyopathy Questionnaire
- PRO Measurement Information System including PROMIS-29, PROMIS-Sexual Function, PROMIS-SF 6a and EQ5D Visual Analogue Scale (VAS)

Funded by the New York Community Trust

Exploratory Objectives: We will explore whether N-of-1 trials can improve decision-making parameters, including decision conflict (measured by the Decision Conflict Scale), patient activation (measured by the Patient Activation Measure), Shared Decision Making (measured by the 9-item Shared Decision-Making Questionnaire), and attitudes toward deprescribing (measured by the revised patient attitudes toward deprescribing questionnaire).
Funded by National Institute on Aging

Primary Endpoints:

The features of a feasible and pragmatic protocol for deprescribing N-of-1 trials as measured by qualitative interviews.
Funded by the National Institute on Aging

All of the below endpoints are being funded by the New York Community Trust.
The change in physical activity when on beta-blocker versus when off beta-blocker, as measured by step count on a wearable activity monitoring device.
The change in lower extremity function when on beta-blocker versus when off beta-blocker, as measured by Short Physical Performance Battery
The change in exercise capacity when on beta-blocker versus when off beta-blocker, as measured by peak oxygen consumption (VO2) during cardiopulmonary exercise test (CPET)

Secondary Endpoints:

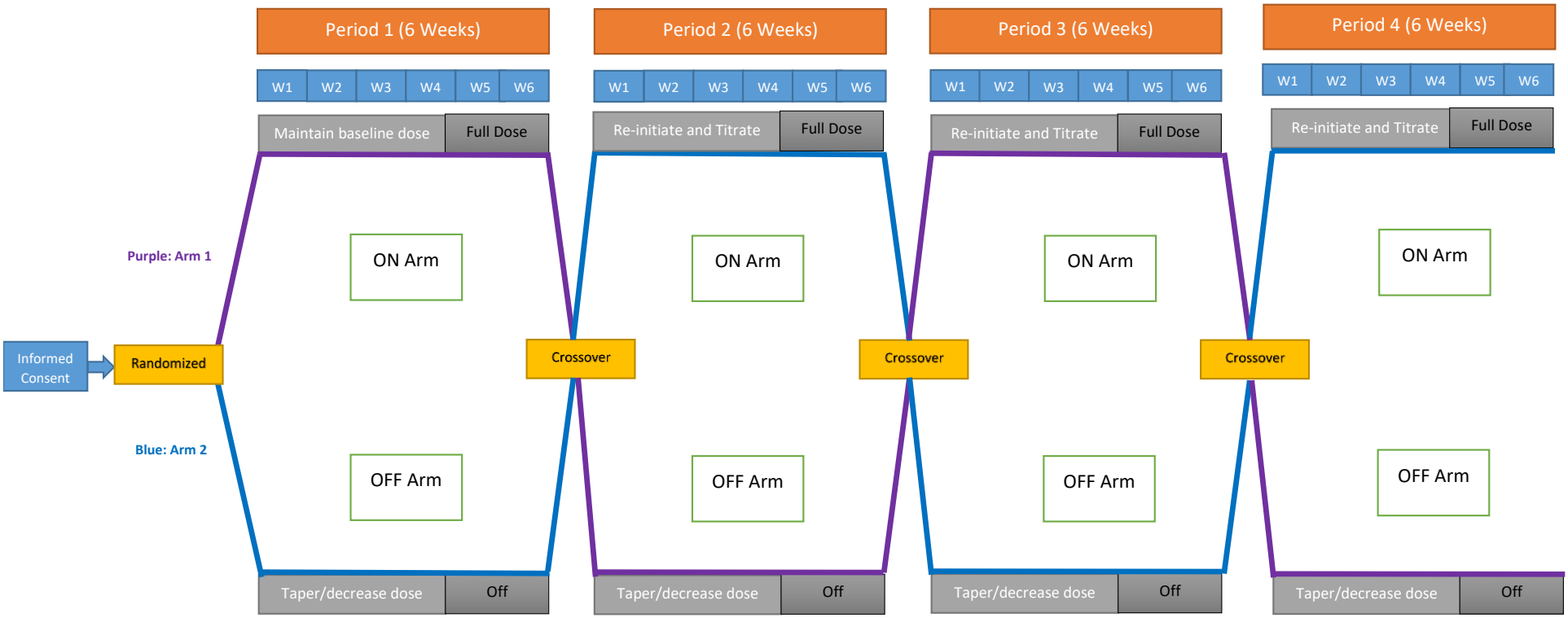
All of the below endpoints are being funded by the New York Community Trust.
The change in patient-reported quality of life when on beta-blocker versus when off beta-blocker, as measured by Patient Reported Outcome Measurement System-29 (PROMIS-29)
The change in patient-reported sexual function when on beta-blocker versus when off beta-blocker, as measured by Patient-Reported Outcome Measurement Information System-Sexual Function (PROMIS-Sexual Function)
The change in patient-reported cognitive function when on beta-blocker versus when off beta-blocker, as measured by Patient-Reported Outcome Measurement Information System-Short Form 6a (PROMIS SF-6a)
The change in patient-reported health status when on beta-blocker versus when off beta-blocker, as measured by Kansas City Cardiomyopathy Questionnaire (KCCQ-12)
The change in patient-reported health when on beta-blocker versus when off beta-blocker, as measured by the EuroQol-5d Visual Analogue Scale (EQ-5D VAS)

Exploratory Endpoints:

The impact of N-of-1 trials on decision conflict as measured by the Decision Conflict Scale.
The impact of N-of-1 trials on patient activation as measured by the Patient Activation Measure.
The impact of N-of-1 trials on Shared Decision Making as measured by the 9-Item Shared Decision-Making Questionnaire.
The impact of N-of-1 trials on attitudes toward deprescribing as measured by the Revised Patient Attitudes toward Deprescribing Questionnaire.

1.1 Schema

Figure 1. Study Design of a subject with 4 six-week periods



1.2 Study Objectives

1.2.1 Co-Primary Objectives

- To determine the features of a feasible and pragmatic protocol for deprescribing N-of-1 trials in patients with Heart Failure with Preserved Ejection Fraction. (Funded by the National Institute on Aging)
- The change in physical activity when on beta-blocker versus when off beta-blocker, as measured by step count on a wearable activity monitoring device. (Funded by the New York Community Trust)
- The change in lower extremity function when on beta-blocker versus when off beta-blocker, as measured by Short Physical Performance Battery. (Funded by the New York Community Trust)
- The change in exercise capacity when on beta-blocker versus when off beta-blocker, as measured by peak oxygen consumption (VO2) during cardiopulmonary exercise test (CPET). (Funded by the New York Community Trust)

1.2.2 Secondary Objectives

- The change in patient-reported quality of life when on beta-blocker versus when off beta-blocker, as measured by Patient Reported Outcome Measurement System-29 (PROMIS-29) (Funded by the New York Community Trust)
- The change in patient-reported sexual function when on beta-blocker versus when off beta-blocker, as measured by Patient-Reported Outcome Measurement Information System-Sexual Function (PROMIS-Sexual Function) (Funded by the New York Community Trust)
- The change in patient-reported cognitive function when on beta-blocker versus when off beta-blocker, as measured by Patient-Reported Outcome Measurement Information System-Short Form 6a (PROMIS SF-6a) (Funded by the New York Community Trust)

Table 1: PRO Administration Details (50 items in total)

Instrument	# of Items	Domain
KCCQ-12	12	HF-specific health status
PROMIS-29	4	Fatigue
	4	Depression
	4	Anxiety
	4	Sleep
	4	Physical function
	4	Social Role
	5	Pain interference/intensity
PROMIS (SF-6a)	6	Cognitive function
PROMIS-Sexual Function	2	Sexual Function
EQ-5D Visual Analogue Scale	1	Quality of Life

- The change in patient-reported health status when on beta-blocker versus when off beta-blocker, as measured by Kansas City Cardiomyopathy Questionnaire (KCCQ-12) (Funded by the New York Community Trust)
- The change in patient-reported health when on beta-blocker versus when off beta-blocker, as measured by the EuroQol-5d Visual Analogue Scale (EQ-5D VAS) (Funded by the New York Community Trust)

1.2.3 Exploratory Objectives

- To examine whether N-of-1 trials can improve decision parameters, patient activation, and attitudes toward deprescribing.
  - Decision Conflict Scale (DCS)
  - Patient Activation Measure (PAM)
  - 9-Item Shared Decision-Making Questionnaire
  - revised Patient Attitudes Toward Deprescribing (rPATD)

2. Background

2.1 Disease

Heart Failure with Preserved Ejection Fraction (HFpEF) affects >3 million people across the US and is a prototypical geriatric syndrome—it disproportionately affects older adults (mean age ~76 years); age-related changes to the cardiovascular system and common age-related comorbid conditions are implicated in its pathogenesis; and multiple comorbid conditions and polypharmacy are nearly universal. While beta-blockers are the most commonly used medication for HFpEF (~80% in a recent Randomized Controlled Trial), there is substantial uncertainty regarding their benefits in HFpEF. Although the benefits of beta-blockers in Heart Failure with reduced ejection fraction are well-documented, Randomized Clinical Trials (RCTs) of beta-blockers in HFpEF have been neutral to date, failing to consistently improve or worsen long-term outcomes including mortality and hospitalization rates; and short-term effects on patient-reported outcomes like function and quality of life are not well-described, with a signal of harm in some.

2.2 Rationale

High medication burden among older adults with multiple chronic conditions including those with heart failure is a growing problem in the United States that can negatively impact the health and wellbeing of older adults. Deprescribing (or medication discontinuation) has emerged as a strategy to improve outcomes in older adults with multiple chronic conditions and high medication burden but is underutilized. With this project, we will refine an innovative pragmatic subject-centered approach (N-of-1 trials) to medication optimization in older adults, thereby improving the health and wellbeing of older adults with multiple chronic conditions.

In Dr. Goyal's clinical experience as Director of the HFpEF Program for the Aging, he has found that some patients feel better with beta-blockers while others feel worse. This idea is supported by opposing pathophysiologic mechanisms highlighted in the literature—on the one hand, beta-blockers can slow down heart rate, improve left ventricular filling, and thus improve cardiac output and overall functioning. On the other hand, beta-blockers can exacerbate chronotropic incompetence, worsen cardiac output, and reduce exercise tolerance. Beta-blockers are also a common cause of adverse drug reactions and can worsen function in some older adults. There is no readily discernable way to determine which patients will feel better and which will feel worse. Although the benefits of beta-blockers in HF with reduced ejection fraction are well documented, RCTs of beta-blockers in HFpEF have been neutral to date, failing to consistently improve or worsen long-term outcomes including mortality and hospitalization rate. Thus, beta-blocker use in HFpEF is a well-suited and clinically relevant model for developing a subject-centered approach to medication optimization.

N-of-1 trials offer a potentially transformative approach to deprescribing. Unlike traditional population-based clinical trials, N-of-1 trials are conducted within a single subject, using multiple crossover design experiments to compare different treatments.

2.3 Risk/Benefit Assessment

The risks and benefits of N-of-1 trials relate directly to the risks of initiation and discontinuation of beta-blockers.

2.3.1 Known Potential Risks

All subjects:
i) Risks associated with down-titration/discontinuation of beta-blocker: Adverse drug withdrawal events including tachycardia, worsened hypertension, palpitations, diaphoresis, shortness of breath, heart failure exacerbation, angina, myocardial infarction, cerebrovascular accident, arrhythmia, hospitalization, and death (shown to occur with abrupt cessation of beta-blocker)
ii) Risks associated with beta-blocker use (and re-initiation/up-titration): Adverse drug events or adverse drug reactions including bradycardia, heart block, hypotension, dizziness, fatigue, depression, confusion, heart failure exacerbation, cerebrovascular accident, hospitalization, and death
iii) Risks associated with wearing the Garmin wearable device: Local skin irritation, wrist pain
iv) Risks associated with subject interviews: Emotional distress related to answering interview questions, and breach of confidentiality
v) Risks associated with Cardiopulmonary Exercise Test and Short Physical Performance Battery: musculoskeletal injury, arrhythmias, acute coronary syndrome, hemodynamic instability, cardiovascular collapse, death.
vi) Risks associated with Short physical performance battery: falling, musculoskeletal injury.
vii) Risks associated with the 6-minute walk test: fatigue, dizziness.
viii) Risks associated with blood draws: pain or bruising, dizziness, infection at the site of the blood draw

2.3.2 Known Potential Benefits

For some, continuing beta-blockers may be beneficial: Beta-blockers slow down heart rate, improve left ventricular filling and thus improve cardiac output and overall functioning. They can function as anti-hypertensive and may suppress arrhythmias.

For others, stopping beta-blockers may be beneficial: Beta-blockers can exacerbate chronotropic incompetence, worsen cardiac output, and reduce exercise tolerance. Beta-blockers are also a common cause of adverse drug reactions and can worsen function in some older adults. Beta-blockers can also contribute to undesirable symptoms like fatigue and sexual dysfunction.

Subjects may specifically benefit from this study by gaining insight on the individual-level short-term effects of beta-blockers. This information could then help subjects determine whether they wish to continue or discontinue beta blockers, potentially contributing to increased decision confidence and subject activation, and possibly improving quality of life.

2.3.3 Assessment of Potential Risks and Benefits

Rationale to exposing subjects to risk
1.) Exposure to beta-blocker: Subjects are already on beta-blocker at the time of recruitment; thus, being on beta-blocker does not explicitly add additional risk beyond usual clinical care
2.) Down-titration/discontinuation: Subjects will have their beta-blocker dose decreased and/or discontinued. There is limited data to support the benefits of beta-blocker in HFpEF, despite its frequent use. Moreover, beta-blocker use poses several harms in older adults including bradycardia, heart block, hypotension, dizziness, fatigue, depression, confusion, heart failure exacerbation, cerebrovascular accident, hospitalization and death. Accordingly, down-titration/discontinuation of beta-blocker may actually be safer than continuing beta-blocker, at least in some.

To mitigate the risks of down-titration/discontinuation, we will incorporate the following:
1.) remote monitoring protocol that includes assessments of resting heart rate and blood pressure
2.) telephone calls made by the research team to the subject on the day before a dose modification is planned, to instruct about the next day's dose change; the day a dose modification is planned, to confirm the dose change was made and the assess health status; and the day following dose modification, to reassess health status, where we will ascertain whether the subject is experiencing any withdrawal effects such as chest pain, tachycardia, palpitations, diaphoresis, and shortness of breath, as well as any adverse events, such as hospitalizations and/or adverse cardiovascular events, including HF exacerbation, myocardial infarction, arrhythmia, cerebrovascular accident and death; based off of subject feedback, telephone calls may be eliminated during the last 2 weeks of each period
3.) We will also provide a 24 hour/7 day per week hotline for subjects to call if they develop any concerning symptoms. Importantly, we will exclude subjects with other indications for beta-blocker use to maximize safety. For example, individuals with hypertrophic cardiomyopathy will be excluded, since beta-blockers have a clear benefit in this condition (and are a Class I indication).

We hypothesize that there will be benefits to dose reduction (down-titration/ discontinuation). Beta-blockers can exacerbate chronotropic incompetence, worsen cardiac output, and reduce exercise tolerance, as well as possibly worsen physical function, and be a major cause of adverse drug reactions. Dr. Goyal (as a board-certified heart failure physician and HFpEF specialist) has already observed this in his clinical practice—among nine subjects in whom he has discontinued beta-blockers, 8 of the 9 felt better.

The justification of risk is that this study has the potential to lead to a paradigm shift in the way beta-blockers are used in HFpEF. We believe beta-blockers are overused in this subtype of heart failure and may be causing more harm than good in the many HFpEF subjects.

In addition, all inclusion and exclusion criteria were selected to ensure we exclude subjects with other evidence-based indications for beta-blockers. In other words, we excluded subjects who may be harmed if we stop beta-blockers.

3. Study Design

3.1 Overall Design

This single site, NIH Stage I of Behavioral Intervention Development trial will extend principles of subject-centered care (a pillar of caring for older adults with MCC) to medication management by producing a broadly applicable approach (N-of-1) that can bypass the inherent limitations of randomized controlled trials which provide average treatment effects and limited data on the effects of medication for a single individual; and thereby facilitate personalized pharmacotherapy and therapeutic precision by determining the optimal therapy for the individual in the face of the inherent complexity and heterogeneity of older adults related to variability in clinical phenotype, drug metabolism, responsiveness to therapy, and health priorities.

This study will also formalize a process that can increase subject involvement and incorporate shared decision making into medication management, an important priority in cardiovascular medicine.

We will conduct N-of-1 trials using a two-arm crossover withdrawal/reversal design (On [A] vs Off [B]) with up to 4 periods. Subjects will be randomized to either Arm1/ABAB or Arm2/BABA (see Figure 1 above). After the initial period (Period 1), each subject will crossover to the other arm and continue in that arm for up to 6 weeks (Period 2). This may be repeated for two more periods for a total of 4 periods; each period will last up to 6 weeks, permitting sufficient time for up-titration and onset of drug action, and down-titration and washout. If the subject and the principal investigator make a final decision to discontinue or continue the beta-blocker at the end of a period, the end of intervention phase will begin at the end of that period visit. For the remainder of the protocol, we refer to "end of intervention" as period 4, but this can be changed based on when a final decision is made about the beta-blocker. The end of intervention visits can occur at any of the periods. The minimum number of periods will be 2 (AB or BA). If the subject wishes to collect more data, then additional periods may be added in an alternating fashion (ABAB or BABA). Accordingly, the number of periods will be an adaptive component of the protocol.

For dose reduction, we will follow a schedule that was safe in a prior deprescribing trial—50% reduction every week until Off[1]. This reduction schedule will follow up-titrations and down-titrations outlined in section 7.4, but will also be adaptive based on subject clinical profiles and symptoms while on and off beta-blockers.

Subjects randomized to Arm 1/ABAB (starting with On[A]), will continue their home dose during Period 1. They will then crossover to Period 2, where we will begin dose reduction. The dose will be reduced by 50% each week until the subject is off of beta-blockers. At the end of period 2 visit, subjects will be given the opportunity to decide if they would like to remain on or off their beta-blocker, or if they would like to continue into period 3. If they chose to continue to period 3, they will restart beta-blocker by starting a low dose and then doubling this dose every week until reaching their

1 Luymes CH, Poortvliet RKE, van Geloven N, de Waal MWM, Drewes YM, Blom JW, Smidt N, Assendelft WJJ, van den Hout WB, de Ruijter W, Numans ME. Deprescribing preventive cardiovascular medication in patients with predicted low cardiovascular disease risk in general practice - the ECSTATIC study: a cluster randomized non-inferiority trial. BMC Med. 2018;16(1):5.

home dose. During Period 4 (last period), we will again conduct a dose reduction, reducing each dose by 50% for a week, until the subject is off of beta-blockers.

Arm 1			
Week 1-6	Week 7-12	Week 13-18	Week 19-24
ON (A)	OFF (B)	ON (A)	OFF (B)
Arm 2			
Week 1-6	Week 7-12	Week 13-18	Week 19-24
OFF (B)	ON (A)	OFF (B)	ON (A)

Table 2. Design for Arm 1 & Arm 2 for a subject completing 4 six-week periods

For patients in Arm 1, the number of periods a subject will complete is dependent on their decision about continuing or discontinuing their beta-blocker at their end of period 2 or end of period 3 visit. If a subject decides they would like to continue their beta-blocker after period 2, they will complete a period 3 to allow for safe up-titration. End of period visits, including the end of intervention period, may be conducted either remotely or in person, based on subject preference and the current status of the COVID-19 pandemic. End of period and end of intervention visits conducted remotely will not have the following physical assessments associated with it: Cardiopulmonary Exercise Test, Short Physical Performance Battery, blood draw, physical assessment, six-minute walk test, and an EKG. Subjects in Arm 1/ABAB who want to stop their beta-blocker can complete their end of intervention visit at period 2 and enter follow-up.

Subjects randomized into Arm 2/BABA will start with Off[B]. Instead of abruptly stopping beta-blocker, these subjects will have their previously prescribed home beta-blocker dose reduced by 50% each week, until the subject is completely off beta-blocker. During Period 2, they will restart beta-blocker by starting a low dose and then doubling this dose every week until reaching their home dose. During Period 3, we will again conduct a dose reduction, reducing each dose by 50% for a week, until the subject is off of beta-blockers. Finally, they will restart beta-blocker by starting a low dose and then doubling this dose every week until reaching their home dose (Similar to Period 2). See Figure 1 above. Regarding patients in Arm 2, if a subject decides they would like to stop their beta-blocker after period 2, they will complete a period 3 to allow for safe down-titration. End of period visits, including the end of intervention period, may be conducted either remotely or in person, based on subject preference and the current status of the COVID-19 pandemic. End of period and end of intervention visits conducted remotely will not have the following physical assessments associated with it: Cardiopulmonary Exercise Test, Short Physical Performance Battery, blood draw, physical assessment, six-minute walk test, and an EKG. Subjects in Arm 2/BABA who want to continue their beta-blocker can complete their end of intervention visit at period 2 and enter follow-up.

We will incorporate an adaptive study design, where each subject will have the option to participate in less (2-3) or more periods (5-6) depending on whether they need additional information to make an informed decision about continuing or discontinuing their beta-blocker at the end of this trial.

Subjects will wear a Garmin wearable device for the duration of the study to collect data on step count to quantify physical activity. We may collect additional data that is captured by the wearable devices, such as floors climbed, distance traveled and calories burned. We may eliminate the use of wearable devices per subject feedback.

Subjects will also undergo a non-invasive cardiopulmonary exercise test (CPET) at the end of period 1 and at the end of period 2 to assess exercise parameters including peak oxygen consumption. In

addition, they will undergo the short physical performance battery at baseline and at the end of each intervention period. The study team will discuss the components of the CPET with the subjects prior to their end of period visits.

Through a pre-existing remote monitoring program at Weill Cornell Medicine, we will provide subjects with a computer tablet and blood pressure cuff free-of-charge. This will allow us to collect vital sign data, including blood pressure and heart rate. We will encourage subjects to collect data up to 3 times per week. Based on patient reports of any concerning symptomatology, we may encourage increased frequency of assessments at different time points of the study. Also, based on prior experience, some subjects may want to collect data more frequently, which will allow. This approach was developed based on our preliminary data from 9 prior N-of-1 trials, where there were no serious adverse events and based on subject feedback (Several subjects requested reduced frequency of required vital sign assessment). If we encounter "Red Flags" (Table 3), we will call the subject to assess symptoms and determine the need for medical attention and/or study withdrawal.

Table 3. Red Flags triggering phone call		
	Upper Limit	**Lower Limit**
Blood Pressure	>160/90 mmHg	<100/60 mmHg
Resting Heart Rate	>100 bpm	<60 bpm

Remote monitoring will occur on a daily basis. Subjects will be provided with a tablet computer and blood pressure cuff free-of-charge. These data will be automatically uploaded to an online portal, which we will review weekly.

Subjects will complete subject-reported outcome questionnaires on quality of life, cognitive function, and sexual function at regular intervals set by each of the validated instruments during the intervention stage via their tablet computers, over the phone, or via email.

The interventions in this study will be used for either exploratory purposes or integrated with study visits to help subjects make decisions on whether they would like to continue or discontinue their beta-blocker medications. CPET and the respective results, RPM vitals (including blood pressure and heart rate), collected blood biomarker levels, step count analysis, and 6-minute walk test results and analysis will serve as exploratory measurements. Therefore, these results and values will not be explicitly shared with the subjects throughout the study to minimize bias. This way, subjects can base their decision-making on how they truly felt (measured by symptom and decision-making questionnaires) and their ability to make an informed decision with their provider. PROs, or subject reported outcomes will be included in the consenting process and study visits. These PROs include answers to their questionnaires and data visualizations analyzing how their answers differed between periods. The PROs will be explicitly discussed with the subjects to further motivate them to make an informed decision on how they feel. These expectations on what will be provided throughout the study will be clearly outlined during the consent process and baseline visit. If subjects specifically request to see these values, the PI and study team will consider providing these results for clinical purposes and per standard of care.

We will also conduct brief qualitative interviews to assess the understandability and usability of materials at each of the following time points: 1) completion of informed consent, 2) completion of each period of the intervention arms, 3) completion of the full intervention phase for each subject, and 4) at 6, 9, and 12-month post end of intervention follow-up periods. Interviews may be conducted via phone call or via Zoom, based on subject preference. The study team will audio record

these interviews. All qualitative interviews will be transcribed by a professional transcribing service. Names and all other PHI that appear in the transcription will be replaced with a generic participant ID or redacted. Additional interviews may be conducted to elicit additional information related to themes previously discussed during interviews and/or feedback provided to the study team during the course of the study.

Per subject feedback, we may eliminate the use of wearable devices or modify subject reported outcome questionnaires. We may also give caregivers the opportunity to share any feedback they may have. We will ask the subjects for permission to discuss the study with their caregivers. We will also ask the subjects for permission to contact and discuss the trial with their primary care provider or their primary cardiologist.

At the conclusion of the intervention phase, and possibly at the end of each intervention period, we will provide subjects with visual analogies of their physical function and subject reported outcomes data. These data will be discussed with them to help them determine if they would like to continue or discontinue their beta-blockers for the foreseeable future.

3.2 Scientific Rationale for Study Design

In Dr. Goyal's clinical experience as Director of the HFpEF Program for the Aging, he has found that some subjects feel better with beta-blockers while others feel worse. This idea is supported by opposing pathophysiologic mechanisms highlighted in the literature—on the one hand, beta-blockers can slow down heart rate, improve left ventricular filling, and thus improve cardiac output and overall functioning. On the other hand, beta-blockers can exacerbate chronotropic incompetence, worsen cardiac output, and reduce exercise tolerance. Beta-blockers are also a common cause of adverse drug reactions and can worsen physical function in some older adults. There is no readily discernable way to determine which subjects will feel better and which will feel worse. Thus, beta-blocker use in HFpEF is a well-suited and clinically relevant model for developing a subject-centered approach to medication optimization.

3.3 Justification for Dose

During the initial "On" [A] period, the target dose will be the one that was prescribed by their usual physician at the time of study enrollment. Justification for the tapering dose is provided above (determined in consultation with other HFpEF experts and pharmacologists; also, this schedule was used in a prior deprescribing study that included beta-blockers).

3.4 End of Study Definition

A subject is considered to have completed the study upon completion of all phases of the study, including the last visit or the last scheduled procedure shown in the **Schedule of Assessments (SoA), Section 6.1**. The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial.

4. Subject Selection

4.1 Study Population

Subjects with a diagnosis of HFpEF, who are patients at Weill Cornell Medicine, and meet all inclusion and exclusion criteria, will be eligible for participation in this study.

4.2 Inclusion Criteria

1. Ambulatory adults age ≥65 years with HFpEF according to ACC/AHA guidelines (signs and symptoms of Heart failure AND ejection fraction ≥50%)
2. Taking beta-blocker

4.3 Exclusion Criteria

1. Alternate causes of HFpEF Syndrome:
    a. Severe aortic stenosis and mitral stenosis
    b. Constrictive pericarditis
    c. High Output HF
    d. Infiltrative cardiomyopathy
2. Other compelling indication beta-blocker
    a. Prior EF <50%
    b. Hypertrophic cardiomyopathy
    c. Angina symptoms
    d. Acute coronary syndrome, myocardial infarction or coronary artery bypass surgery in prior 3 years
    e. History of ventricular tachycardia
    f. Atrial arrhythmia with hospitalization for rapid ventricular response, prior 1 year
    g. Sinus tachycardia >100 bpm, atrial arrhythmia with ventricular rate >90 beats per minute, systolic blood pressure >160 mmHg
3. Clinical instability (N-of-1 trials are appropriate for stable conditions only)
    a. Decompensated heart failure
    b. Hospitalized in past 30 days
    c. Medication changes or procedures in prior 14 days that could confound observations/data, at PI discretion
4. Estimated life expectancy <6 months
5. Moderate-severe dementia or psychiatric disorder precluding informed consent
6. Any condition that, in Principal Investigator's opinion, makes the patient unsuitable for study participation

4.4 Lifestyle Considerations

Not applicable.

4.5 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE). We are not anticipating any screen failures, as only eligible subjects (based on pre-screening) will be consented. All subjects will be randomized upon gaining consent (no additional screening procedures are necessary).

In the instance of a screen failure, we will not re-screen the subject in the future.

4.6 Strategies for Recruitment and Retention

Subjects will be recruited primarily from the HFpEF Program at Weill Cornell Medicine. Cardiology, Geriatrics, and Primary Care clinics may be screened in addition if necessary. Approximately 70% of patients seen between July 2018-October 2019 in the HFpEF clinic would be eligible to participate. By 2020 the HFpEF Program will see >200 unique patients, which will provide a sufficient number of subjects to enroll from. We plan to enroll 16 subjects.

The research assistant will screen subjects scheduled in the HFpEF Program in advance of their appointments to identify potentially eligible subjects. The research assistant will then introduce the study to each eligible subject and conduct the informed consent process. A screening and enrollment log will be kept by the research assistant. Subjects will receive $50 upon consenting, randomization, and completing the baseline assessment. All subjects will provide written informed consent and HIPAA notifications.

We will not enroll the following vulnerable populations:

- Pregnant women
- Children
- Those who lack capacity to consent
- Employee/student volunteers

Planned enrollment is estimated based on frequencies observed in the HFpEF Program at Weill Cornell Medicine. Frequencies in the HFpEF Program are as follows:

- 57% Women
- 62% White non-Hispanic
- 16% Black non-Hispanic
- 11% Hispanic/Latino

Strategies for Retention: There are several opportunities to engage subjects to ensure retention. We will contact subjects weekly to instruct them to complete standardized web-based patient-reported outcomes questionnaires. Subjects will be asked to complete these assessments on their tablet computer (which we will provide free-of-charge and has internet capabilities), over the phone, or via email. We will also conduct routine phone calls for safety purposes (at this time, we can remind subjects to complete the weekly assessments if needed). For subjects who do not complete the assessments (we will track this electronically), we will call them daily to remind them and/or assist them with completing the assessments over the phone. If we are unable to contact the

subject over the phone, when applicable, we will attempt contact via email. To ensure pragmatism and enhance retention, assessments will be short and subject to change per subject feedback. Based off of subject feedback, we may eliminate subject phone calls on the last two weeks of each period. To maximize compliance and retention, subjects will receive $50 at the end of successful completion of each phase up to 4 total phases (baseline and the 4 treatment periods). They will receive an additional $50 as a compliance bonus at the end of period 4/end of study. In total, **subjects** will receive up to $300. We will define compliance as attending 100% of scheduled visits and completing 90% of assessments during the defined time period.

Subjects may receive reimbursement for unanticipated fees, per PI discretion.

5. Registration Procedures

5.1 Subject Registration (WCM only)

Subjects will be registered within the WRG-CT as per the standard operating procedure for Subject Registration.

6. Study Procedures

6.1 Schedule of Assessments

	Baseline	Research Intervention Phase					Post Intervention Phase		
		Daily	Weekly	Biweekly	End of Periods 1-3	End of Intervention Phase (Period 4)	6 Month Follow-up	9 Month Follow-up	12 Month Follow-up
Informed Consent									
Randomization									
Demographics									
Medication Inventory									
Baseline Beta-Blocker Use									
Physical Exam									
Central Blood Pressure									
Electrocardiogram									
Cardiopulmonary Exercise Test[2]									
Blood Draw for Troponin & NT-proBNP[3]									
Blood Draw for Future Research[4]									
Six-Minute Walk Test									
Short Physical Performance Battery									
Qualitative Interview							☎	☎	☎
Typology Question									
Health Literacy									
Number Literacy									
Short Graph Literacy									
Data Preferences									
EQ5d-VAS									
PROMIS-29							☎	☎	☎
PROMIS-SF 6A							☎	☎	☎
PROMIS-Sexual Function							☎	☎	☎
KCCQ-12							☎	☎	☎

2 Cardiopulmonary Test to occur only at the end of Period 1 and Period 2. Cardiopulmonary test to be accompanied by a blood draw for NT-proBNP and Troponin.
3 Blood samples will be collected for Troponin and NT-proBNP at the end of each period. In addition, on visits where the subject performs a Cardiopulmonary Test, we may collect blood for Troponin and NT-proBNP directly after the cardiopulmonary test.
4 Optional component of this study. Blood will be drawn at baseline, as well as at the end of Period 1 and Period 2

Decision Making Outcomes Questionnaires[5]									
Dose Modification			☎						
Telephone Call[6]			☎						
Step Count Collection									
Remote Monitoring									
Interim Events History			☎				☎	☎	☎
Assessment of Beta-Blocker Usage							☎	☎	☎

Legend	
	In-Office visit
	Conducted Remotely
☎	Conducted via Telephone
	Collected via Garmin wearable device

5 Decision Making Parameters Questionnaire to consist of Decision Conflict Scale, Decision Conflict Subscales, Patient Activation Measures Survey, Shared Decision-Making Questionnaire (SDM-1-9) and Revised Patient Attitudes Towards Deprescribing (rPATD)
6 Telephone contact to occur the day prior to, the day of, and the day following a dose modification. Telephone calls may be eliminated per subject feedback during the last two weeks of each period.

6.1.1 Baseline In-Person Visit

- Informed consent
- Randomization
    - Eligible subjects will be randomly assigned to into Arm 1 (ABAB) or Arm 2 (BABA) with a 1:1 ratio using a computer-generated randomization scheme developed by the data manager. Arm 1 will be on an On-Off-On-Off (ABAB) drug scheme, while Arm 2 will be Off-On-Off-On (BABA)
- Demographics
- Medication Inventory
- Baseline beta-blocker use
- Physical Exam, including vital signs
- Central blood pressure assessment via the UScom BP+ device
    - This device measures central and brachial blood pressure and blood pressure waveforms at the heart, as well as in the arm.
- Electrocardiogram
- Blood draw for Troponin & NT-proBNP
- Blood draw for future research
- Six-Minute Walk Test
- Exercise test used to assess aerobic capacity endurance. The distance covered over 6 minutes is used as the outcome by which to compare changes in performance capacity.
- Short Physical Performance Battery
    - Combines the results of gait speed, chair stand and balance tests as a predictive tool for possible disability and can aid in the monitoring of function in older people
        - Gait Speed: assesses the subject's lower extremity function
        - Chair Rise: assesses core strength
        - Balance Test: assess the subject's ability to stand unassisted without the use of a cane or walker
- Qualitative interview on understandability of study purpose and design
- Typology Questionnaire
- Health Literacy Questions
- Number Literacy Questions
- Short Graph Literacy
- EQ5D Visual Analogue Scale
- PROMIS-29
- PROMIS-SF 6A
- PROMIS-Sexual Function
- KCCQ-12
- Decision Making Outcomes Questionnaires
    - Decision Conflict Scale
    - Decision Conflict Subscale
    - Patient Activation Measure (PAM) Survey
    - Shared Decision Making Questionnaire
    - Revised Patient Attitude Towards Deprescribing Questionnaire (rPATD)

6.1.2 Treatment Phase

6.1.2a Daily

- Remote Monitoring
    - Remote monitoring will collect vital sign data, including blood pressure and heart rate via a free of charge remote monitoring platform already in use in the HFpEF Program. Data will be reviewed weekly. If we encounter "Red Flags", we will call the subject to assess symptoms, and determine the need for medical attention and/or study withdrawal in consultation with the subject's other physicians and the DSMB.
        - Red Flags are as follows:
            - Blood pressure >160/90 mmHg or <100/60 mmHg
            - Heart Rate >100 bpm or <50 bpm
- Step Count
    - Daily step count will be collected via Garmin wearable devices that will be provided to subjects during the duration of the treatment phase of the trial.

6.1.2b Weekly

- Dose modification (as described in section 3.1)
- Telephone Contact on the day prior to the dose modification, the day of the dose modification and on the day following dose modification. Telephone calls may be eliminated during the last 2 weeks of each period per subject feedback.
- Patient Reported Outcomes (PROMIS-29, PROMIS-SF 6A) via web-based surveys taken at home on tablet computers provided to each subject, over the phone, or via email – frequency/length of surveys may be decreased per subject feedback
- Interim Events History (Adverse Events/SAE) will be asked during each phone call

6.1.2.c Biweekly

- Kansas City Cardiomyopathy Questionnaire (KCCQ-12)

6.1.2d End of Periods

- Medication Inventory
- Dose Modification
- Physical Exam, including vital signs
- Central blood pressure assessment via the UScom BP+ device, when possible
- Electrocardiogram
- Six Minute Walk Test
- Cardiopulmonary Exercise Test (at the end of Period 1 and Period 2)
    - We may draw additional blood for Troponin & NT-proBNP directly after the CPET. On visits which include a CPET, the subject may have Troponin and NT-proBNP drawn twice.
- Blood Draw for Troponin & NT-proBNP
- Blood draw for future research (at end of period 1 & end of period 2 only)
- Short Physical Performance Battery
- Qualitative interview on understandability and usability of study materials
- EQ-5D VAS
- PROMIS-29
- PROMIS-SF 6A
- PROMIS-Sexual Function

- Kansas City Cardiomyopathy Questionnaire (KCCQ-12)
- Interim Events History

6.1.2e End of Intervention Visit Period

- Medication Inventory
- Dose Modification
- Physical Exam
- Central blood pressure assessment via the UScom BP+ device
- Electrocardiogram
- Six Minute Walk Test
- Short Physical Performance Battery
- Qualitative interview on understandability and usability of study materials
- Typology Question
- EQ5D-VAS
- PROMIS-29
- PROMIS-SF 6A
- PROMIS-Sexual Function
- Kansas City Cardiomyopathy Questionnaire (KCCQ-12)
- Interim Events History

6.1.2f Unscheduled Visits

Unscheduled visits may be performed at any time during the study. The unscheduled visits may occur on-site or as a telephone visit. All data recorded during unscheduled visits will be recorded in REDCap. Depending on the reason for the unscheduled visit, appropriate assessments will be performed based on the judgement of the investigator and the results will be recorded in the REDCap.

6.1.3 Follow-up Phase

Six, nine, and twelve months after the end of intervention, the study team will access the subject's electronic health record to assess the following:

- Interim Events History
- Determine whether subjects are taking beta-blockers or not
- PROMIS-29
- PROMIS-SF 6A
- PROMIS-Sexual Function

The study team will conduct a phone call or Zoom meeting with the subject to review this information and confirm survey completion. Surveys will be sent out to the subjects the week of their six-, nine-, and twelve-month follow-ups via their tablet computer provided by the study team, through email, or over the phone. A qualitative interview will also take place at the 6, 9, and 12-month follow up periods. This qualitative interview will be audio recorded and transcribed by a professional transcribing service. We will store the audio recordings obtained from the interviews three years after data analysis completion. These recordings will then be erased permanently.

Positive indications from study participants about a hospitalization or possible events at other institutions will be followed by collection of selected medical records. Records will include administrative hospital codes and copies of relevant portions of the medical record, including

admission and discharge notes, progress notes, laboratory studies, ECGs, radiographic studies, and any other diagnostic testing or procedure notes. We will obtain an appropriate consent for release of information prior to obtaining medical records.

For patients who have expired prior to the time of first contact for consent, we will contact the next of kin to obtain authorization to request/receive information about the cause of death and hospitalizations/emergency room visits leading up to the patient's death. In this scenario, the next of kin will provide verbal consent and asked to provide a release of medical information form.

7. Study Intervention

7.1 Study Intervention/Device Description

Beta-blockers, also known as beta-adrenergic blocking agents, work by blocking the effects of epinephrine. Although the benefits of beta-blockers in HF with reduced ejection fraction are well documented, RCTs of beta-blockers in HFpEF have been neutral to date, failing to consistently improve or worsen long-term outcomes including mortality and hospitalization rate. Beta-blockers do not provide symptomatic improvement in all subjects; some may feel better while other may feel worse after initiating this drug class. This is supported by opposing pathophysiologic mechanisms highlighted in the literature—on the one hand, beta-blockers can slow down heart rate, improve left ventricular filling, and thus improve cardiac output and overall functioning. On the other hand, beta-blockers can exacerbate chronotropic incompetence, worsen cardiac output, and reduce exercise tolerance. Beta-blockers are also a common cause of adverse drug reactions and can worsen function in some older adults. There is no readily discernable way to determine which patients will feel better and which will feel worse.

All subjects will have been taking beta-blockers prescribed by their physician prior to enrollment. The study team will provide the subjects dosage instructions based on the down-titration/up-titration schedule outlined in this protocol.

The study team will not provide study drug to the subjects. Subjects will continue to obtain their beta-blockers in the same manner as prior to study enrollment.

Beta-blockers may be contraindicated in the following subjects:

Relative contraindications:

- Asthma; COPD (use cardio-selective β blockers/β-1 selective)
- Psoriasis
- Symptomatic bradycardia
- Sick sinus syndrome (without a pacemaker); heart block greater than first degree
- Peripheral artery occlusive disease, Raynaud phenomenon
- Pregnancy
- Atenolol is absolutely contraindicated in pregnancy

Absolute contraindications:

- Allergy
- Cardiogenic shock and hypotension
- Pheochromocytoma

These contraindications are less relevant because these issues would have already been considered by their usual prescribing physicians prior to the study. To be clear, we will not be initiating a new prescription of beta-blocker for subjects; all subjects enrolled will have already be prescribed beta-blocker at the time of enrollment into the study.

7.2 Availability

Subjects will have been prescribed beta-blockers by their physician. Subjects will thus continue to obtain their beta-blockers in this manner. When modifications are made to the dosage, the study team will advise if their tablet or pill may be halved. In instances where the pill cannot be halved, the study team will prescribe a new dosage, which will be sent to the subject's pharmacy.

7.3 Acquisition and Accountability

Prescriptions for beta-blocker may be provided by prescribers in the HFpEF Program as needed.

7.4 Dosing and Administration

We have created a down-titration schedule, where we will reduce the dose of each beta-blocker by 50% every week, a schedule used in a prior deprescribing study of antihypertensives, that included beta-blockers. This schedule accounts for a sufficient number of half-lives to ensure drug clearance and accounts for changes in receptor density and related adrenergic hypersensitivity linked to withdrawal symptoms and ADWEs observed after abrupt beta-blocker cessation. Re-initiation/up-titration will be done in reverse order. Subjects will never go on a dosage higher than their usual home dose. All drugs will be administered orally. To assist subjects with dose reduction, each subject will receive pill cutters.

Table 4: Examples of drug down-titration schedule for selected β-blockers

Examples	Week 1	Week 2	Week 3	Week 4	Week 5+6
Metoprolol 200mg daily	100mg daily	50mg daily	25mg daily	12.5mg daily	*Off*
Carvedilol 50mg BID	25mg BID	12.5mg BID	6.25mg BID	3.25mg BID	*Off*
Bisoprolol 10mg daily	5mg daily	2.5mg daily	*Off*	*Off*	*Off*
Atenolol 100mg daily	50mg daily	25mg daily	12.5mg daily	*Off*	*Off*
Betaxolol 20mg daily	10mg daily	5mg daily	2.5mg daily	*Off*	*Off*
Nebivolol 40mg daily	20mg daily	10mg daily	5mg daily	*Off*	*Off*
Nadolol 320mg daily	160mg daily	80mg daily	40mg daily	*Off*	*Off*
Propranolol 40mg BID	20mg BID	10mg BID	5mg BID	*Off*	*Off*
Acebutolol 600mg BID	300mg BID	150mg BID	75mg BID	*Off*	*Off*
Penbutolol 80mg daily	40mg daily	20mg daily	10mg daily	*Off*	*Off*
Pindolol 30mg BID	15mg BID	7.5mg BID	*Off*	*Off*	*Off*
Labetalol 1200mg BID	600mg BID	300mg BID	150mg BID	*Off*	*Off*

7.4.1 Dosing Delays/Dose Modifications

We do not anticipate any dosing delays or dose modifications outside of the aforementioned down-titration and up-titration schedule. However, dosing changes and other adaptations to the dosing schedule will be up to the discretion of the PI if clinical findings arise.

7.5 General Medication Inventory and Supportive Care Guidelines

All concomitant medications will be recorded and/or updated on subject medication log throughout the course of the study.

7.6 Duration of Therapy and Criteria for Removal from Study

We do not anticipate treatment delays. In the setting of a treatment delay due to an adverse event, continued study participation will depend on:

- Disease progression
- Intervening illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Subject decision to withdraw from the study,
- General or specific changes in the subject's condition render the subject ineligible for further treatment in the judgment of the investigator.

7.7 Duration of Follow Up

Six, nine, and twelve months after the end of intervention we will access the electronic health record to assess vital status, hospitalizations, emergency department visits and whether or not the subject is taking a beta-blocker.

7.8 Measures to Minimize Bias: Randomization and Blinding

This study will not be blinded. The study team will conduct randomization using a WCM-approved randomization tool.

7.9 Study Intervention/Follow-up Compliance

Study team will ensure the protocol is followed as written. Protocol can be modified per subject feedback.

Remote monitoring will occur on a daily basis. Subjects will be provided with a tablet computer and blood pressure cuff free-of-charge. These data will be automatically uploaded to an online portal, which we will review weekly.

Telephone calls will occur on a weekly basis, during each call we will request information regarding drug compliance. Telephone calls may be eliminated during the last 2 weeks of each period. If unable to contact the subject via telephone, we will attempt through email.

For subjects that are potentially lost to follow-up, we will make at least four attempts to contact them, in a 4-week time frame, via telephone and/or email. We will also inquire about their status from their physician, as well as through their electronic health records.

A subject will be considered lost to follow-up if we are unable to contact them after 4 attempts in 4 weeks.

7.10 Blood for Future Research

Subjects will be given the opportunity to participate in a voluntary component of the study, where we will draw blood samples for future research. Subjects will be informed of risks, benefits and alternatives. Up to 30 ml of blood will be obtained. For subjects who have a blood specimen that is insufficient in volume, a repeat blood draw may be performed at their next visit.

Blood draws for future research will follow similar processing and storage procedures as outlined in a companion WCM-approved IRB (Protocol 19-05020216 – Next Generation Sequencing & Molecular Characterization of Cardiovascular Diseases) that supports the HFpEF/Cardiovascular biobank.

Subjects who consent to this additional component will have an additional 2 tubes of blood drawn at the baseline visit, as well as at the end of period 1 and end of period 2.

8. Study Intervention Discontinuation and Subject Discontinuation/Withdrawal

8.1 Discontinuation of Study Intervention

If consented subjects are intolerant or unwilling to proceed with dose modification, we will continue to follow them through the course of the study (if subject is willing). Remaining study procedures will be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator will determine if any change in subject management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- Concomitant Medications
- Decision making outcomes questionnaire
- Short Physical Performance Battery
- Adverse Events/SAE

8.2 Subject Discontinuation/Withdrawal from the Study

Subjects are free to withdraw from participation in the study at any time if they wish.
An investigator may discontinue or withdraw a subject from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject (this will be decided on conjunction with their own physician and/or the DSMB).
- Disease progression which requires discontinuation of the study intervention
- If the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Subject lost to follow-up after several attempts to contact subject to schedule study visit.

The reason for subject discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF) in REDCap. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will be replaced.

8.3 Lost to Follow Up

A subject will be considered lost to follow-up if we are unable to contact them after four attempts in 4 weeks.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site will attempt to contact the subject, reschedule the missed visit within five business days, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subjects. These contact attempts will be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. Correlative/Special Studies

Not applicable.

10. Measurement of Effect

Not applicable

11. Data Reporting / Regulatory Considerations

11.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, and efficacy data for all enrolled subjects.

11.1.1 REDCap

REDCap (Research Electronic Data Capture) is a free data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group-based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced, and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

11.1.2 Smart Watches, Tablet Computers and Internet Capable Devices

Subjects will be provided with Garmin wearable devices. Garmin devices will function as a typical Garmin device. Data will be exported from the Garmin devices directly onto an ITS-tagged, WCMC-issued computer. It will then be transferred onto our WCMC server and deleted from the computer. We will codify data in order for us to conduct data analysis and to share with subjects and their physicians.

Although the devices will be used primarily to collect step-count, we will collect all relevant health data the device provides, including, but not limited to calories burned, floors climbed, and distance traveled.

Phillips internet capable tablet computers will be provided to subjects for remote monitoring. These devices are already in use in the HFpEF Program.

11.2 Regulatory Considerations

11.2.1 Institutional Review Board/Ethics Committee Approval

As required by local regulations, the Investigator will ensure all legal aspects are covered, and approval of the appropriate regulatory bodies obtained before study initiation.
Before initiation of the study, the protocol, the ICF, other written material given to the subjects, and any other relevant study documentation will be submitted to the appropriate Ethics Committee. Written approval of the study and all relevant study information must be obtained before the study center can be initiated. Any necessary extensions or renewals of IEC/IRB approval must be obtained for changes to the study, such as amendments to the protocol, the ICF, or other study documentation. The written approval of the IEC/IRB together with the approved ICF must be filed in the study files. The Investigator will report promptly to the IEC/IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The Investigator will submit written summaries of the study status to the IEC/IRB as required. On completion of the study, the IEC/IRB will be notified that the study has ended.

All agreed protocol amendments will be clearly recorded on a protocol amendment form and will be signed and dated by the original protocol approving signatories. All protocol amendments will be submitted to the relevant institutional IEC/IRB for approval before implementation, as required by local regulations. The only exception will be when the amendment is necessary to eliminate an immediate hazard to the trial subjects. In this case, the necessary action will be taken first, with the relevant protocol amendment following shortly thereafter. Weill Cornell Medicine must approve all consent form changes prior to local IRB submission. Relevant study documentation will be submitted to the regulatory authorities of the participating countries, according to local/national requirements, for review and approval before the beginning of the study. On completion of the study, the regulatory authorities will be notified that the study has ended.

11.2.2 Ethical Conduct of the Study

The Investigators and all parties involved should conduct this study in adherence to the ethical principles based on the Declaration of Helsinki, GCP, ICH guidelines and the applicable national and local laws and regulatory requirements.

This study will be conducted under a protocol reviewed and approved by the applicable ethics committees and investigations will be undertaken by scientifically and medically qualified persons, where the benefits of the study are in proportion to the risks.

11.2.3 Informed Consent

The investigator or qualified designee must obtain documented consent according to ICH-GCP and local regulations, as applicable, from each potential subject or each subject's legally

authorized representative prior to participating in the research study. Subjects who agree to participate will sign the approved informed consent form and will be provided a copy of the signed document.

The initial ICF, any subsequent revised written ICF and any written information provided to the subject must approved by IRB prior to use. The ICF will adhere to IRB/IEC requirements, applicable laws and regulations.

11.2.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor-Investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

11.2.5 Record Retention

Essential documents are those documents that individually and collectively permit evaluation of the study and quality of the data produced. After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file.

12. Statistical Considerations

To provide statistics to the subjects when sharing key outcomes, we will compare PROs between Periods A (On) and Periods B (Off) using a linear or generalized linear mixed effects model that will include the fixed effects of beta-blocker, treatment effect (A vs B), period effect (1, 2, 3, 4 etc.) and a patient-level random intercept to account for within-patient repeated measurements. The period fixed effect will estimate the effects of down-titration/up-titration and the time-dependent treatment effect will estimate On vs. Off effect. We will also explore period-specific fixed effects for treatment and compare the models using Akaike Information Criterion. As an exploratory analysis, we will also test the pattern of activity as a function of time in specialized statistical models called functional data model.

Power: The study team will have 80% power to detect a within-patient difference of 1.1 standard deviations in the four outcomes at an α=1.67% (after controlling for Type I error inflation due to three outcomes). While power for these analyses will be modest, they will provide pilot data necessary for a future proposal to the National Institute of Health (NIH) and/or Patient-Centered Outcomes Research Institute (PCORI) to conduct a larger multi-center randomized controlled trial to determine whether discontinuation of BB in HFpEF can improve outcomes relevant to older adults including function and quality of life.

Power: The co-primary objective is to determine features of a feasible and pragmatic protocol for deprescribing N-of-1 trials, which will be done through an iterative stakeholder-engaged process (C.1.2). The goal is *not* to establish safety and/or efficacy here. Thus, power calculations for this Aim are less relevant.

12.1 Study Design/Endpoints

We will collect data on physical function, patient-reported outcomes, decision parameters, patient activation, and attitudes toward deprescribing.

12.2 Sample Size/Accrual Rate

We plan to enroll one subject/month for 16 months.

12.3 Stratification Factors

Not applicable

12.4 Analysis of Endpoints

12.4.1 Analysis of Endpoints

The study team will compare the On-arm to the Off-arm for the 4 main outcomes of interest—vitals collected via remote monitoring, step-count, peak oxygenation uptake, short physical performance battery score, and patient-reported outcome domains. To achieve this, analysis will use a general linear mixed effects model, where fixed effects of BB, period effect (Period 1 or Period 2) and carry-over effect will be included. In addition, a patient-level random intercept will be added to the model to account for within-patient repeated measurements. To control for inflation of Type I error due to testing multiple outcomes, the Holm's stepdown procedure will be used. The overall Type I error will be set at 5% and all statistical analyses will be two-sided.

1. *Vitals collected via Remote Monitoring*. A general linear mixed effects model will be used, comparing daily pulse and blood pressure averages of the On and Off arms. The study team will analyze data from the timeframe during which BB is completely stopped ("Off" when participating in the Off-arm) and at usual dose ("Full dose" when participating in the On-arm); this will occur during the last 2 weeks each Period (see Figure 1). The study team will utilize a general analytic framework to analyze average blood pressure and pulse during each period.

2. *Physical activity (via step-count).* A general linear mixed effects model will be used, comparing daily step-count averages of the On and Off arms. The study team will analyze data from the timeframe during which BB is completely stopped ("Off" when participating in the Off-arm) and at usual dose ("Full dose" when participating in the On-arm); this will occur during the last 2 weeks of each Period (see Figure 1). The study team will utilize a general analytic framework to analyze average daily step-count during each period. As an exploratory analysis, the study team will also perform analysis that will visualize and test the pattern of activity as a function of time in specialized statistical models called functional data model developed for this purpose. The study team will then test the differences in the properties of these curves between the two treatment groups.

3. *Function (via short physical performance battery).* A general linear mixed effects model will be used, comparing the short physical performance battery score of the On and Off arms.

4. *Exercise capacity (via peak oxygen consumption during exercise).* A general linear mixed effects model will be used, comparing VO2 of the On and Off arms.

5. *Patient-reported outcomes (PROs).* A general linear mixed effects model will be used, comparing each patient-reported outcome domain (HF-specific quality of life, fatigue, depression, anxiety, sleep, physical function, social role, and pain) of the On and Off arms. The study team will analyze data from the timeframe during which BB is completely stopped ("Off" when participating in the Off-arm) and at usual dose ("Full dose" when participating in the On-arm); this will occur during weeks 5 and 6 of each Period, or the last two weeks of the period. (see Figure 1).

6. *Subject Qualitative Interviews.* Directed content analysis methods will be used to develop relevant categories and themes from interview transcript data. Coding will be conducted through the coding platform Dedoose. Transcripts will be analyzed by two team members, consulting additional members to establish consensus where needed. Inter-rater reliability between coders will be established using a Cohen's Kappa score.

To provide statistics to the subjects when sharing key outcomes, we will compare PROs between Periods A (On) and Periods B (Off) using a linear or generalized linear mixed effects model that will include the fixed effects of beta-blocker, treatment effect (A vs B), period effect (1, 2, 3, 4 etc.) and a patient-level random intercept to account for within-patient repeated measurements. The period fixed effect will estimate the effects of down-titration/up-titration and the time-dependent treatment effect will estimate On vs. off effect. We will also explore period-specific fixed effects for treatment and compare the models using Akaike Information Criterion. As an exploratory analysis, we will also test the pattern of activity as a function of time in specialized statistical models called functional data model.

12.5 Interim Analysis

We will primarily conduct analysis and track AE/SAEs in anticipation of our DSMB meetings. We will also conduct analysis of the primary and secondary endpoints. The DSMB will review the study outcomes in an unmasked fashion (study is not blinded).

12.6 Reporting and Exclusions

12.6.1 Evaluation of Toxicity

Not applicable

12.6.2 Evaluation of Response

Not applicable.

13. Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by subjects or observed by investigators or research staff.

13.1 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

13.1.1 Investigational Agent or Device Risks (Expected Adverse Events)

Adverse events are not expected, but the following are risks are possible:

i) Risks associated with down-titration/discontinuation of beta-blocker: Adverse drug titration events including tachycardia, worsened hypertension, palpitations, diaphoresis, and shortness of breath, heart failure exacerbation, angina, myocardial infarction, cerebrovascular accident, arrhythmia, hospitalization, and death (shown to occur with abrupt cessation of beta-blocker)
ii) Risks associated with beta-blocker use (and re-initiation/up-titration): Adverse drug events or adverse drug reactions including bradycardia, heart block, hypotension, dizziness, fatigue, depression, confusion, heart failure exacerbation, cerebrovascular accident, hospitalization, and death
iii) Risks associated with wearing the Garmin wearable device: Local skin irritation, wrist pain
iv) Risks associated with subject interviews: Emotional distress related to answering interview questions, and breach of confidentiality
v) Risks associated with CPETs: musculoskeletal injury, arrhythmias, acute coronary syndrome, hemodynamic instability, cardiovascular collapse, death
vi) Risks associated with Short physical performance battery: falling, musculoskeletal injury.
vii) Risks associated with the 6-minute walk test: fatigue, dizziness.
viii) Risks associated with blood draws: pain or bruising, dizziness, infection at the site of the blood draw

13.1.2 Adverse Event Characteristics and Related Attributions

The following procedures will be used to document adverse events:

A vignette will be created describing the i) date of the event, ii) the date that study personnel became aware of the event, iii) clinical circumstances surrounding the event including precipitating events, iv) action taken by study personnel including treatment, and v) outcome of the event. This will be documented by PI Goyal.

Adverse events will be graded per Common Terminology Criteria for Adverse Events version 5.0 criteria. Grade refers to the severity of the AE.

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[7]
Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[8]
Grade 4: Life-threatening consequences; urgent intervention indicated
Grade 5: Death related to AE

Relatedness of the AE: This will be determined by Dr. Goyal, by using the following:

- Definitely Related
- Probably Related
- Possibly Related
- Not Related to the Research

Expectedness of the AE: This will be determined by Dr. Goyal (Yes/No):

- Unexpected: Those that differ from AEs highlighted in Section 13.1.1 in nature, severity or frequency
- Expected: Those consistent with AEs highlighted in Section 13.1.1 in nature, severity, or frequency

13.1.3 Recording of Adverse Events

All adverse events will be recorded on a subject specific AE log. The AE log will be maintained by the research staff and kept in the subject's research chart.

13.1.4 Reporting of AE to WCM IRB and DSMB

All AEs occurring on this study will be reported to the WCM IRB according to the WCM IRB policy, which states that **expected and unexpected** adverse events, grades 3-5, should be reported on the Adverse Event & IND Safety Reporting Cumulative Table. These AEs will be reported at continuing review.

Adverse events which meet ALL of the following 3 conditions will be reported within 7 calendar days of PI awareness:

1. The harm is "unexpected" when its specificity and severity are not reflected in the informed consent form; AND
2. The harm is "related" or "possibly related" AND
3. The harm that places subjects at a greater risk of harm than previously known or recognized

7 Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
8 Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

WCM DSMC

All Adverse events which meet ALL of the following 3 conditions will be reported within 7 calendar days of PI awareness:

1. The harm is "unexpected" when its specificity and severity are not reflected in the informed consent form; AND
2. The harm is "related" or "possibly related" AND
3. The harm that places subjects at a greater risk of harm than previously known or recognized

13.1.5 Reporting Events to Subjects

Not applicable. We are not performing diagnostic studies; we do not anticipate any incidental findings.

AEs and SAEs will not be reported directly to subjects, unless otherwise instructed to by the DSMB. (All AEs and SAEs will be reported to the DSMB.)

13.1.6 Events of Special Interest

Not applicable.

13.1.7 Reporting of Pregnancy

Not applicable.

13.2 Definition of SAE

An SAE is defined by the ICH guidelines as any AE fulfilling at least one of the following criteria:

- Fatal
- Life threatening: refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe
- Requiring in-patient hospitalization or prolongation of existing hospitalization.
- Resulting in persistent or significant disability or incapacity
- Congenital anomaly or birth defect
- Medically significant: refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered to be SAEs when, based upon medical judgement, they may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The following reasons for hospitalization are not considered as SAES:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons
- Hospitalization for pre-planned surgery or standard monitoring of a pre-existing disease or medical condition that did not worsen

13.2.1 Reporting of SAE to IRB & DSMC

WCM IRB:
All SAEs occurring in this study will be reported to the IRB according to the IRB policy. IRB policy states that SAEs should be reported within 7 days if the following criteria are met:

- The SAE is unexpected and not reflected in the ICF
- The SAE is related or possibly related
- The SAE places subjects at a greater risk of harm than previously known or recognized

At yearly continuing reviews, all AEs and SAEs grade 3-5 that are either expected or unexpected must be reported.

WCM DSMC:
Immediate reports for SAEs will be submitted to the DSMC within 7 calendar days of PI awareness if they meet all the following criteria:

1. The harm is "unexpected" when its specificity and severity are not reflected in the informed consent form; AND
2. The harm is "related" or "possibly related" AND
3. The harm that places subjects at a greater risk of harm than previously known or recognized

13.2.2 Reporting of SAE to FDA [For Protocols Where WCMC is the Sponsor-Investigator]

Not applicable.

13.3 AE/SAE Follow Up

In addition to reporting all adverse events, the study team will take all appropriate measures to ensure that subjects will have access to necessary medical care. Any acute change in medical condition will be reported to the subject's physician for follow-up care. All information about the study will be provided to the caring physician. As this study is not blinded, there will be no masking issue with regard to providing optimal medical care. All study procedures will be discontinued at the treating physician's request, the subject's request, and/or as judged appropriate by the principal investigator. In the case of any emergency situation, the study physicians will institute any emergency aid needed and then make arrangements for transportation to the Emergency Department. All research subjects will have access to medical care if an adverse event occurs. The subject and/or the insurance carrier will be billed for this care. Subjects will not receive special compensation for injury solely because they are subjects in the study. All subjects are fully informed about this policy as part of the informed consent process.

For SAEs that are determined to be "possibly related" or "related", the subject will be assessed, evaluated, and treated for any potential recurrence and according to the seriousness of the symptoms. Based on the information gathered, it will then be determined whether the subject should be removed from the study or continue their participation.

13.4 Time Period and Frequency for Event Assessment and Follow Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study subject presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the subject is screened will be considered as baseline and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study coordinator or the principal investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization. The following table provides examples of actions that may be taken following selected adverse events.

Adverse Event	**Typical Action**
Hospitalization	Medical management including beta-blocker management as recommended by treating physician. If hospitalization unrelated to study and not contraindicated following discussion between investigators and hospital care team, subject will continue to follow protocol while hospitalized.
Worse or new arrhythmia	Emergent care if indicated including admission and necessary medications/interventions. Subject withdrawal from the study.
Cerebrovascular accident	Emergent care if indicated including admission and necessary medications/interventions. Subject withdrawal from the study.
Myocardial infarction	Emergent care if indicated including admission and necessary medications/interventions. Subject withdrawal from the study.
Angina	Emergent care if indicated including admission and necessary medications/interventions. Subject withdrawal from the study.
Heart failure exacerbation	Emergent care if indicated including admission and IV diuretics. For non-emergent issues, standard review and adjustment of medications. Medical management including beta-blocker management as recommended by treating physician. If exacerbation unrelated to the study and not contraindicated following discussion between investigators and treating physician, subject will continue to follow protocol.
Shortness of breath	Evaluation of volume status, adjustment of medications. Medical management including beta-blocker management as recommended by treating physician. If exacerbation unrelated to the study and not contraindicated following discussion between investigators and treating physician, subject will continue to follow protocol.
Worsened hypertension	Emergent care if indicated including admission and IV antihypertensive agents. For non-emergent issues, standard review and management of oral medications. If unrelated to the study and not contraindicated following discussion between investigators and treating physician, subject will continue to follow protocol.

14. Unanticipated Problems Involving Risks to Subjects or Others

14.1 Definition of Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO)

[The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

14.1.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPIRTSOs) to the reviewing Institutional Review Board (IRB). The UPIRTSO report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UPIRTSO;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UPIRTSO.

To satisfy the requirement for prompt reporting, UPIRTSOs will be reported using the following timeline:

- UPIRTSOs that are serious adverse events (SAEs) will be reported to the IRB and to the DSMB within 3 days of the investigator becoming aware of the event.
- Any other UPIRTSO will be reported to the IRB and to the DCC/study sponsor within 7 days of the investigator becoming aware of the problem.

15. Data and Safety Monitoring Plan (DSMP)

We plan to use the WCM DSMB for this trial, as this a resource provided to the WCM scientific community, and they have the necessary expertise and infrastructure to act as a DSMB for this trial. All AEs and SAEs will be reported to the DSMB. AEs where the harm is unexpected, the harm is "related" or "possibly related," and the harm suggests that the research places subjects at greater risk of harm than previously known, an immediate report will be submitted within 7 calendar days of the PI awareness. We will record seriousness, relatedness and expectedness of the adverse event, as determined by Dr. Goyal. We will

report when the AE occurred, as well as when the study team became aware of the AE. We will collect any medical documentation pertaining to the AE. If treatment must be stopped, this determination will be made by Dr. Goyal with the subject. Because all subjects will have been on study drug before initiating the trial, and we will not exceed their home dose, we do not anticipate having to terminate study treatment.

The DSMB will convene to review the study data after each cohort of 4 subjects.