The Inorganic Nitrate for Exercise in Heart Failure (iNIX-HF) Trial

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Background:

Heart Failure (HF) is a major public health problem when considering the incidence, prevalence, mortality rate, and costs to the patient and the health care system. According to the American Heart Association (AHA), it is estimated that there are over 5.1 million people in the United States (US) and 23 million people worldwide affected by HF.[1, 2] One in nine deaths is due to heart failure, and 50 percent of people who have heart failure will die within the first 5 years of diagnosis. HF costs the healthcare system in the US $32 billion dollars annually in missed workdays, medications, and heath care services.[1] A contributing factor to this cost is that surviving patients with heart failure have a higher burden due to the debility HF causes compared to those without heart failure. The debility is so profound that the New York Heart Association classification system of HF is based on the severity of the patient's inability to exercise and perform activities of daily living. Given the disabling nature of HF and its impact on both the patient as well as the healthcare system, any improvement in exercise capacity or tolerance would be of benefit.

There is emerging data from our group and others that dietary nitrate, particularly in nitrate-rich foods such as beetroot juice (BRJ), increases plasma NO_3^- levels, plasma NO_2^- levels, and breath NO levels.[3-5] This increase in NO improves exercise performance even in patients with HF.[3] This improvement in performance is due to several physiologic effects of NO. It is a vasodilator and helps improve muscle perfusion. NO also increases muscle power and speed of contraction through its actions on cGMP.[6] Thus, dietary *INORGANIC* nitrate in beetroot juice appears to be a novel treatment with which to attack the disabling effects of heart failure.

Unfortunately, BRJ has potential unwanted side effects, which might limit its use on a large scale. First, the taste is bitter, earthy, and salty. One reviewer of a grant even remarked that it was "unfit for human consumption". Second, the juice can cause beeturia and red-colored stools, which may make patients think they are bleeding or may mask true internal bleeding. Next, beetroot juice is high in oxalate; thus, its chronic consumption may increase kidney stone formation. Lastly, it is administered as 2/3 of a cup of liquid, so it is by nature less portable. Thus, there is a clear need for a new form of delivery for inorganic nitrate for patients with HF.

Therefore, potassium nitrate (KNO_3) is an intriguing alternative for delivery of inorganic nitrate to subjects with HF. Dietary inorganic nitrate in KNO_3 as a source of NO has several advantages over the classical nitric oxide synthase production pathway (L-arginine), current pharmacologic *ORGANIC* nitrates, sildenafil, and beetroot juice (see Table 1. below). Ten mmol of pharmacy-grade KNO_3 can be put into a single gelatin capsule (gelcap) by the Barnes-Jewish compounding

pharmacy. This is roughly the equivalent of two-thirds of a cup of beetroot juice. The gelcap would be devoid of taste, is portable, does not contain oxalate, and would not cause beeturia or red stools. We also believe that these advantages of KNO_3 will increase medication compliance.

Table 1. KNO3 versus other possible approaches for increasing NO

Current Approaches	Advantages of KNO_3
L-arginine	• Not dependent on NO synthase (NOS) • Functions well in acidic tissues • Functions well in ischemic tissues
Organic, pharmacologic nitrates (e.g., nitroglycerin)	• Does not cause tolerance • Does not increase reactive oxygen species (ROS) in mitochondria • May be less likely to cause hypotension • May be less likely to cause headaches
Sildenafil	• Inadvertent inhibition of PDE6 is thought to be responsible for retinal dysfunction and vision changes • May be less likely to cause hypotension • May be less likely to cause flushing or headache
Beetroot juice	• Does not contain oxalate (decreased risk of kidney stones) • No allergies • No bitter taste • Easier to control exact nitrate content • More portable • No beeturia to be confused with/mask renal/urinary tract disease • No red stool to be confused with/mask gastrointestinal disease

Study Aims:

Aim 1: To determine the optimum dose of inorganic nitrate to improve exercise performance (i.e., aerobic capacity and muscle power) in patients with heart failure and reduced ejection fraction (HFrEF). Aerobic capacity will be assessed by peak oxygen consumption ($\dot{V}O_2$peak) and muscle power will be assessed as maximal knee extensor power using a Biodex machine. This is a double-blind, cross-over study aim in which each participant will receive single doses of potassium nitrate (10 or 20 mmol KNO_3) administered in gelatin capsules in random order one week apart.

Aim 1 Sub-Study: Pharmacokinetics. To determine the time course of effects of a single 10 mmol dose of KNO_3 on plasma nitrate and nitrite concentrations, breath nitric oxide concentration, blood pressure, and heart rate at rest. Blood samples will be drawn before dosing, every hour for 3 hours after KNO_3 ingestion, and at 4.5, 6, 12, 18 (optional), and 24 hours post-dose. Plasma levels of nitrate and nitrite will be quantified using HPLC.

Aim 2: To determine the effects of 2 weeks of inorganic nitrate therapy vs. placebo on aerobic capacity and muscle power in patients with HFrEF. The dose for this aim will be 10 mmol of KNO_3 daily in a single gelatin capsule taken in the morning. This dosing regimen is based on the results of Aim 1, which revealed that the beneficial effects on exercise performance were not statistically different for the 10 and 20 mmol doses taken on one occasion in the morning, whereas tolerability was lower with the 20 mmol dose. The rationale for taking the 10 mmol dose once daily is based on the half-life of KNO_3.

Aim 3: To determine the effects of 6 weeks of inorganic nitrate therapy vs. placebo on aerobic capacity and muscle power in patients with HFrEF. The dose for this aim will be 10 mmol of KNO_3 daily in a single gelatin capsule taken in the morning. This dosing regimen is based on the results of Aim 1, which revealed that the beneficial effects on exercise performance were not statistically different for the 10 and 20 mmol doses taken on one occasion in the morning, whereas tolerability was lower with the 20 mmol dose. The rationale for taking the 10 mmol dose once daily is based on the half-life of KNO_3.

Participants:

Inclusion: Subjects included in this study will be patients ≥18 years of age with documented stable, NYHA class II-IV, non-ischemic heart failure with an ejection fraction <45%. Participants must be on a stable medical regimen that is considered standard of care for HF (e.g., a beta-blocker and ACE-inhibitor/angiotensin receptor blocker) for at least 60 days prior to study. This is required to exclude any patients with reversible causes of cardiac dysfunction. All subjects must be free of any significant orthopedic limitations or other contraindications to strenuous exercise.

Exclusion: Vulnerable populations as defined by the U.S. Department of Health and Human Services, including prisoners and children, will be excluded from this study, as will be women who are pregnant. Those taking pharmacologic (organic) nitrates during the last 3 mo will be excluded, as will be those taking phosphodiesterase inhibitors (e.g., Viagra), as these can potentiate NO effects. Those taking proton pump inhibitors, antacids, or xanthine oxidase inhibitors will be asked to hold these medications for the duration of the study, if approved by his/her physician. These drugs will also be held for at least 5 half-lives before any study-related activity. Otherwise patients taking these drugs will be excluded as these can affect reduction of NO_3^- and NO_2^-. Subjects having active angina/ischemia from epicardial coronary disease, requiring supplemental O_2 at rest or for exercise, will be excluded. Similarly, subjects with systolic blood pressure <95 or >180 mmHg or diastolic blood pressure <40 or >95 mmHg at consent, a plasma K+ level ≥5mEq/L, or an estimated glomerular filtration rate of <45 mL/min based on most recent clinical laboratories will be excluded. Subjects with primary hypertrophic cardiomyopathy, infiltrative cardiomyopathy (e.g., amyloid), active myocarditis, complex congenital heart disease, active collagen vascular disease, more than mild mitral or aortic stenosis, valvular heart disease with severe regurgitation of any valve, or who have undergone percutaneous coronary intervention, new bi-ventricular pacing, or coronary bypass grafting in the last 3 mo will be excluded. Subjects with acute or chronic severe liver disease as evidenced

by encephalopathy, INR>1.7 without anticoagulant therapy, or variceal bleeding will be excluded. Subjects with a terminal disease other than HF with expected survival <1 y will be excluded. Finally, subjects with any major orthopedic, psychiatric, neurological, or other condition that would impair performance of the exercise studies will be excluded.

Methods:

Aim 1: Dose Response of Potassium Nitrate (KNO_3)

The effects of a two different, single doses of KNO_3 on $\dot{V}O_2$peak and maximal muscle power in patients with HFrEF will be evaluated during 2 study visits. The screening visit may be conducted as a separate visit or combined with the first dose visit.

Screening Visit.

1) **Consent**: All study procedures will be reviewed with the participant before he/she provides written informed consent. Consent includes giving permission for the investigators to review their medical records.
2) **Blood Sample**: A blood sample will be drawn for basic screening laboratories, including glucose and creatinine (for estimation of glomerular filtration rate).
3) **Physical Exam**: Subjects will have a brief history and physical examination. These will not be done with participants who have had a physical exam within the past 6 months.
4) **Resting Echocardiogram**: A resting echocardiogram will be performed to enable assessment of cardiac blood flow. An intravenous contrast agent may used to obtain a clearer assessment of cardiac blood flow, if needed. The echocardiogram may not be necessary if the participant had an echocardiogram within the past 12 months.
5) **Questionnaires**: Subjects will be asked to complete two questionnaires: Basic Health Questionnaire and the Minnesota Living with Heart Failure Questionnaire.
6) **Instructions for KNO_3 dose visits**: Subjects will be instructed to refrain from using mouthwash, antacids, proton pump inhibitors, or chewing gum before each KNO_3 dose visit.

KNO_3 Dose Visit 1

1) Subjects will report to the Clinical Translational Research Unit (CTRU) at Washington University**.**
2) **KNO_3 Gelcaps**: Subjects will receive 10 or 20 mmol of KNO_3 in the form of a gelcap.
3) **Blood Samples**: Subjects will have blood drawn (20mL or about 1.5 tbsp). An intravenous catheter will be placed to facilitate blood sampling 5 times during the visit. The first blood sample will be obtained before ingestion of the cap and the others will be obtained once each hour for 4 hours after ingestion of the gelcap. The blood will be used to determine blood levels of nitrate and nitrite. A sample also will be obtained for measurement of blood lipids.
4) **Blood Pressure and Heart Rate**: Blood pressure and heart rate will be measured once before the gelcap is consumed and once each hour for 4 hours after the gelcap is consumed.

5) **Breath Nitric Oxide**: Subjects will exhale into a tube attached to a portable electrochemical analyzer (NIOX VERO, Aerocrine Inc., Morrisville, NC) following the American Thoracic Society/European Respiratory Society guidelines before and 4 times after ingestion of the gelcap. Breath nitric oxide concentration provides a surrogate biomarker of whole-body NO production.
6) **Saliva Sample**: A sample of saliva will be obtained to determine the different types of oral bacteria residing in the mouth, based on bacterial DNA analyses. Some types of bacteria can convert nitrate to nitrite. This will be done only once.
7) **Exercise Test – Maximal Muscle Power**: 2 hours after ingesting the gelcap, subjects will complete the following series of tests to assess leg muscle power. A Biodex 4 isokinetic dynamometer (Biodex Medical Systems, Shirley, NY) will be used to measure maximal voluntary force and power during knee extension exercise performed with the dominant leg at angular velocities of (in order) 0, 1.57, 3.14, 4.71, and 6.28 rad/second, which equate to 0, 90, 180, 270, and 360 °/second. The chair back-chair seat angle will be set to 85° and the dynamometer adjusted to place the axis of rotation of the lever arm adjacent to the lateral femoral epicondyle. To minimize other movement, straps will be placed across the torso, hips, and thigh, and subjects will not be allowed to use the handholds. Range of motion will be determined. Next, the subject will perform 3-4 knee extensions at each velocity, with the isometric testing conducted at an angle of 1.22 rad (70°). Two minutes of rest will be allowed after each group of contractions. Strong verbal encouragement will be provided throughout all portions of the isokinetic testing.
8) **Exercise Test – Aerobic Capacity:** After 10 min of recovery from the muscle power testing, peak oxygen consumption ($\dot{V}O_2$peak) will be determined with an incremental treadmill exercise test to volitional fatigue using the modified Naughton protocol. Subjects will walk on a treadmill and breathe into a mouthpiece while wearing a nose clip (to prevent airflow through the nose). Subjects will be asked to give their maximal effort. Blood pressure and heart rhythm will be monitored. A ParvoMedics TrueOne metabolic cart will be used to measure ventilation (Ve), oxygen consumption ($\dot{V}O_2$), and carbon dioxide production ($\dot{V}CO_2$) throughout exercise. Data from this test will be used to quantify Ve/$\dot{V}O_2$, Ve/$\dot{V}CO_2$, ventilatory threshold (defined using the V-slope method), oxygen uptake efficiency slope (OUES), and $\dot{V}O_2$peak. Subjects will also be asked to give a rating of perceived exertion (RPE) on the Borg scale (6-20) and their perceived dyspnea on a five-point visual-analog scale.

KNO_3 Dose Visit 2

At least 7 days after KNO_3 Dose Visit 1, subjects will receive a different gelcap than they received during Dose Visit 1 (i.e., 10 or 20 mmol KNO_3) and then complete all of the assessments listed under KNO_3 Dose Visit 1 except the saliva sample.

Aim 1 Sub-Study: Pharmacokinetics

To determine the time course of effects of a single 10 mmol dose of KNO_3 on plasma nitrate and nitrite concentrations, breath nitric oxide (NO) concentration, blood pressure, and heart rate at rest. Blood samples will be drawn and breath NO will be sampled before

dosing, every hour for 3 hours after KNO_3 ingestion, and at 4.5, 6, 12, 18 (optional), and 24 hours post-dose.

Screening Visit

1) **Consent:** All study procedures will be reviewed with the participant before he/she provides written informed consent. Consent includes giving permission for the investigators to review their medical records.
2) **Blood Sample:** A blood sample will be drawn for basic screening laboratories, including glucose, K+, and creatinine (for estimation of glomerular filtration rate).
3) **Physical Exam:** Subjects will have a brief history and physical examination. These will not be done with participants who have had a physical exam within the past 6 months.
4) **Resting Echocardiogram**: A resting echocardiogram will be performed to enable assessment of cardiac blood flow. An intravenous contrast agent may used to obtain a clearer assessment of cardiac blood flow, if needed. The echocardiogram may not be necessary if the participant had an echocardiogram within the past 12 months.
5) **Questionnaire**: Subjects will be asked to complete a Health Questionnaire.
6) **Instructions to participants**: Subjects will be instructed to refrain from using mouthwash, antacids, proton pump inhibitors, or chewing gum before the KNO_3 dose visit.

Dose Visit

1) Subjects will report to the Clinical Translational Research Unit (CTRU) at Washington University for either two outpatient visits or a single inpatient (overnight) visit, based on their preferences.
2) **KNO_3 Gelcaps:** Subjects will receive a single KNO_3 gelcap containing 10 mmol of inorganic nitrate.
3) **Blood Samples:** An intravenous catheter will be placed to facilitate blood sampling throughout the visit. The total amount of blood drawn will be ~30 mL (2.0 Tbsp). The first blood sample will be obtained before ingestion of the KNO_3 gelcap and the others will be obtained once each hour for 3 hours after ingestion of the gelcap and at 4.5, 6, 12, 18 (optional), and 24 hours post-dose. If this sub-study is completed as two outpatient visits, then the 18h blood sample is optional and the 24h blood sample will be drawn at the second visit. For inpatient visits, all blood samples will be drawn during this dose visit.
4) **Breath Nitric Oxide:** Subjects will exhale into a tube attached to a portable electrochemical analyzer (NIOX VERO, Aerocrine Inc., Morrisville, NC) following the American Thoracic Society/European Respiratory Society guidelines before and several times after ingestion of the gelcap, on the same schedule as the post-dose blood samples. Breath nitric oxide concentration provides a surrogate biomarker of whole-body NO production.
5) **Blood Pressure and Heart Rate:** Blood pressure and heart rate will be measured once before the gelcap is consumed and several times after ingestion of the gelcap, on the

same schedule as the post-dose blood samples.

Visit 2 (only needed if the dose visit was an outpatient visit)

1) Subjects will report to the Clinical Translational Research Unit (CTRU) at Washington University approximately 23.5 hours after they received the KNO_3 gelcap.
2) **24h Assessments:** The 24h blood sample will be drawn, breath nitric oxide will be assessed, and blood pressure and heart rate will be measured.

Aim 2. Randomized Controlled Trial of Potassium Nitrate (KNO_3) Therapy for 2 Weeks

The effects of KNO_3 therapy on $\dot{V}O_2$peak and maximal muscle power in patients with HFrEF will be evaluated in a randomized, placebo-controlled trial. The KNO_3 dose used in this aim will be 10 mmol daily. The treatment (or placebo) period will be 2 weeks, with measurements of $\dot{V}O_2$peak and maximal muscle power completed before and at the end of the intervention using the same methodology as in Aim 1.

Screening Visit.

The screening visit procedures will be the same as for Aim 1 above. If a subject participated in Aim 1, then he/she will not have to repeat the screening procedures for Aim 2.

Exercise Testing Visit 1.

1) Subjects will report to the Clinical Translational Research Unit (CTRU) at Washington University**.**
2) **Blood Samples**: Subjects will have blood drawn (20mL or about 1.5 tbsp) to determine blood levels of nitrate and nitrite using HPLC. A sample also will be obtained for measurement of potassium and blood lipids.
3) **Blood Pressure and Heart Rate**: Blood pressure and heart rate will be measured once before the gelcap is consumed and once each hour for 4 hours after the gelcap is consumed.
4) **Breath Nitric Oxide**: Subjects will exhale into a tube attached to a portable electrochemical analyzer (NIOX VERO, Aerocrine Inc., Morrisville, NC) following the American Thoracic Society/European Respiratory Society guidelines.
5) **Saliva Sample**: A sample of saliva will be obtained to determine the different types of oral bacteria residing in the mouth, based on bacterial DNA analyses. Some types of bacteria can convert nitrate to nitrite. This will not be done if the subject participated in Aim 1.
6) **Exercise Test – Maximal Muscle Power**: Subjects will complete the following series of tests to assess leg muscle power. A Biodex 4 isokinetic dynamometer (Biodex Medical Systems, Shirley, NY) will be used to measure maximal voluntary force and power during knee extension exercise performed with the dominant leg at angular velocities of (in order) 0, 1.57, 3.14, 4.71, and 6.28 rad/second, which equate to 0, 90, 180, 270, and 360 °/second. The chair back-chair seat angle will be set to 85° and the dynamometer adjusted to place the axis of rotation of the lever arm adjacent to the lateral femoral

epicondyle. To minimize other movement, straps will be placed across the torso, hips, and thigh, and subjects will not be allowed to use the handholds. Range of motion will be determined. Next, the subject will perform 3-4 knee extensions at each velocity, with the isometric testing conducted at an angle of 1.22 rad (70°). Two minutes of rest will be allowed after each group of contractions. Strong verbal encouragement will be provided throughout all portions of the isokinetic testing.

7) **Exercise Test – Aerobic Capacity:** After 10 min of recovery from the muscle power testing, peak oxygen consumption ($\dot{V}O_2$peak) will be determined with an incremental treadmill exercise test to volitional fatigue using the modified Naughton protocol. Subjects will walk on a treadmill and breathe into a mouthpiece while wearing a nose clip (to prevent airflow through the nose). Subjects will be asked to give their maximal effort. Blood pressure and heart rhythm will be monitored. A ParvoMedics TrueOne metabolic cart will be used to measure ventilation (Ve), oxygen consumption ($\dot{V}O_2$), and carbon dioxide production ($\dot{V}CO_2$) throughout exercise. Data from this test will be used to quantify Ve/$\dot{V}O_2$, Ve/$\dot{V}CO_2$, ventilatory threshold (defined using the V-slope method), oxygen uptake efficiency slope (OUES), and $\dot{V}O_2$peak. Subjects will also be asked to give a rating of perceived exertion (RPE) on the Borg scale (6-20) and their perceived dyspnea on a five-point visual-analog scale.
8) **KNO_3 Gelcaps**: Subjects will receive a 2-week supply of KNO_3 gelcaps or placebo gelcaps in a double-blinded manner (i.e., neither the subject nor the investigators will know which gelcap the subject receives).

Exercise Testing Visit 2.

Two weeks after Exercise Testing Visit 1, subjects will report to the Clinical Research Unit (CRU) at Washington University after an overnight fast and repeat all of the procedures that were performed during Exercise Testing Visit 1 (except the saliva sample).

Safety Monitoring:

We will make every effort to minimize risks by observing and monitoring participants during testing and throughout the 2-week and 6-week treatment periods. Emergency equipment and trained personnel are available to deal with an emergency that may arise during assessments in the clinical research unit. The risk of bruising or infection at an IV site will be minimized by having experienced personnel trained in the appropriate sterile techniques place the IVs. Possible risks associated with the echocardiogram procedures include an allergic reaction to the contrast agent, an allergic skin reaction to the electrode gel, and mild discomfort due to the light pressure of the ultrasound probe. The risk of an allergic reaction to the contrast agent will be minimized by not using contrast in anyone with a known allergy, not using contrast unless necessary for adequate image analysis, and monitoring subjects closely after the contrast agent is administered.

If any particular question on a questionnaire makes the subject uncomfortable, he/she may discuss its importance and the need to answer it with the research team member. They may

choose not to answer any question. If a subject has an incidental finding on his/her echocardiogram, blood work, or physical exam that is noted and is clinically important, he/she will be made aware of it through an incidental finding letter. He/she will be advised to share the information with his/her physician.

The data will be reviewed by the PI at least every 6 months. Dr. Edward Geltman will also review the relevant data (events, complaints, and the results of all the study endpoints) at least once each year. The safety monitoring panel is comprised of Edward Geltman, MD; Janet McGill, MD; and Mae Gordon, PhD.

Data Analysis:

Aim 1: Data comparing the 2 doses of KNO_3 on exercise performance, plasma NO_3^-, plasma NO_2^-, and breath NO will be analyzed using two-way (i.e., treatment x time) analysis of variance (ANOVA) for repeated measures using an alpha set at 0.05. In addition, the changes in measured variables will be analyzed using univariable regression methods.

Aim 1 Sub-Study: Pharmacokinetics data from the blood samples will be used to determine the time course and peak plasma concentrations of nitrate and nitrite in response to a single dose (10 mmol) of KNO_3.

Aim 2: Data from the randomized, controlled trial of 2 weeks of KNO3 treatment will be analyzed using analyses of covariance in which the post-treatment value of the outcome measure will be the dependent variable and the pre-treatment value and the study group will be the independent variables. Additional analyses will adjust for sex as a covariate. The mean and standard deviation of the pre- to post-treatment change in the two outcome measures (i.e., $\dot{V}O_2$peak and maximal muscle power) will serve as a guide for power calculations in the subsequent RCT for which this application is a prelude. In all analyses of covariance, regression residuals will be evaluated so we can assess the fit of the model. If the model fit is poor, we will explore data transformations that improve the fit and, if such transformations cannot be found, it is possible that we will analyze the data using semi parametric methods based on the ranks of the data. Since experience suggests that both outcome measures tend to be normally distributed, it is unlikely that these alternative approaches will prove necessary.

Sample Size Estimation:

Aim 1: Sample sizes were estimated using data from our previous beetroot juice (BRJ) study, in which the BRJ beverage contained 11.2 mmol of nitrate. Based on average breath NO measured 1 hour, 2 hours, and 3 hours after consuming the BRJ, breath NO increased 12 +/- 11 ppb in response to 11.2 mmol nitrate, for an effect size of 1.1. If we assume a comparable increase with a KNO_3 capsule relative to placebo, then approximately 6 subjects would be sufficient to provide a power of more than 0.9 at alpha=0.05. However, a larger sample size will be needed to determine the effects of different doses of the KNO_3 capsule on exercise performance, plasma NO_3^-, and plasma NO_2^-, as these have not been studied previously. To be conservative

and based on what we know about variability in exercise tolerance among HF patients, we will enroll 25 subjects, with the goal of obtaining complete data on 20 subjects. Power calculations were performed using G*Power 3.1.9.2.

Aim 1 Sub-Study: The sample size will be approximately 10 participants.

Aim 2: While this aim is not designed to reach statistical significance with adequate power, we have performed power computations to estimate the magnitude of the improvement in the two outcomes (i.e., $\dot{V}O_2$peak and maximal muscle power) that could be detected with 10 subjects in each group. Those computations are based on two-sided tests at the 0.05 level of significance. Our preliminary aerobic capacity data indicate that HFrEF patients will have a baseline $\dot{V}O_2$peak value of 22.5±5.5 mL/kg/min. Given these data, the power to detect an increase in $\dot{V}O_2$peak of 32.4% will be 0.8; the power to detect an increase in $\dot{V}O_2$peak of 37.8% will be 0.9. Our preliminary muscle power data suggest that HFrEF patients will have a mean baseline maximal knee extensor power of 4.2±1.1 W/kg. Using these data and 10 subjects per group, the power will be 0.8 if the magnitude of the increase in knee extensor power is 35.7%; the power will be 0.9 if the increase in knee extensor power is 40.5%.

References:

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