Study Protocol and Statistical Analysis Plan

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Introduction

This section outlines the key statistical considerations for the human studies aspects of the grant proposal. For each of our specific aims we provide outlines for the analysis plans, along with corresponding rationale for choice of study deign with associated sample sizes.

Study Design

The main study design is that of randomized clinical trial assessing the effects of 3 months of resistance exercise (RE) training relative to a sedentary control (SC) condition in insulin resistant (IR) study volunteers. A total of 48 IR individuals meeting inclusion/exclusion criteria as outlined in the application will be enrolled. Baseline measures will be obtained after which they will be randomized in a 2:1 ratio to RE (n=32) versus SC (n=16). After 3 months, baseline measures will be repeated, with the expectation of improvements in measures in the RE-trained arm.
We will additionally recruit a group of 16 insulin sensitive (IS) individuals, in whom the same measures will be obtained, at baseline only.

Rationale for Randomized Trial Design

Initially it may seem that a single arm study whereby all individuals receive RE training would be sufficient to answer the questions of interest; however, by including a sedentary control group, if measures increase in the RE-trained group, but not in the SC group, we will have more confidence that the training is causative of the changes. It is possible that some measures may change over time, for example consequent to seasonal effects.
Rationale for Randomization Ratio

In order to be as efficient in our design, we propose a 2:1 randomization ratio; we devote relatively more resources to the RE training arm, as the individuals receiving RE training are of primary interest. In addition to learning whether our measures of interest change over time in this group (and relative to the sedentary control group), we will seek to explore the extent to which changes in some measures relate to others and this will benefit from as large a sample size as possible; in contrast there is relatively little to be learned from the control group other than to check that there are no changes of consequence over the 3 month study time period in this group.

Rationale for Insulin Sensitive Comparator Group

The premise underlying the proposal is that insulin resistance can to some extent be ameliorated by RE training. It is thus important to demonstrate that (i) key measures of interest actually do differ in IR people compared to IS people, and (ii) that any changes in these measures with RE training do indeed differ in the expected direction – closer to those of IR people. Although we do not dramatic changes with only 3 months of training, it will be of additional benefit to be able to quantify, even if informally, the proportional

extent to which improvements can be made in measures relative to the group of IS people that we recruit.

Procedures for Randomization and Blinding
We will create a dynamic randomization allocation algorithm structured to minimize imbalance with respect to key baseline variables including age and sex. This will be implemented with a web interface in a SAS application with restrictions so that access is granted only on a need-to-know basis. The study statistician will be able to monitor assignments globally to ensure the algorithm is working appropriately and the study coordinator (with a back-up) will be able to log in to access randomization assignment for each individual study participant on a prospective basis. All members of the research team involved in obtaining any of the measures will be blinded (to the extent possible) to the assignment of individuals to study arms. Those study team members involved in training will, of course, not be blinded. Randomization assignment data will be merged with the rest of the study data according to study identification numbers only as needed for analysis, otherwise they will remain separate until the studies are completed.

Statistical Analysis
Aim 1 - Change in muscle strength
Endpoint: Δ(1RM normalized to lean mass) = [1RM at 3 months / DEXA lean mass at 3 months] − [1RM at baseline / DEXA lean mass at baseline].
Primary analysis: Two-sample t-test (RE vs SC) on Δ normalized 1RM.

Aim 2 - Change in insulin sensitivity
Endpoint: Δ(Insulin AUC) where AUC (μIU·min/mL) is computed from time points −20, 0, 10, 20, 30, 60, 90, 150, 240 min using the trapezoidal rule.
Primary analysis: Two-sample t-test (RE vs SC) on ΔAUC.

Aim 3 - Change in lean mass
Endpoint: Δ total lean mass (kg) by DEXA.
Primary analysis: Two-sample t-test (RE vs SC) on Δ lean mass.

Aim 4 - Change in body fat percentage
Endpoint: Δ total body fat percentage by DEXA.
Primary analysis: Two-sample t-test (RE vs SC) on Δ fat %.

Aims 1-4 data will be presented as mean Δ±SD in RE vs SC and p-value.