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Study in Parkinson Disease of Exercise (SPARX): Translating high-intensity exercise from animals to humans

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ABSTRACT

A burgeoning literature suggests that exercise has a therapeutic benefit in persons with Parkinson disease (PD) and in animal models of PD, especially when animals exercise at high intensity. If exercise is to be prescribed as "first-line" or "add-on" therapy in patients with PD, we must demonstrate its efficacy and dose–response effects through testing phases similar to those used in the testing of pharmacologic agents. The SPARX Trial is a multicenter, randomized, controlled, single-blinded, Phase II study that we designed to test the feasibility of using high-intensity exercise to modify symptoms of PD and to simultaneously test the nonfutility of achieving a prespecified change in patients' motor scores on the Unified Parkinson Disease Rating Scale (UPDRS). The trial began in May 2102 and is in the process of screening, enrolling, and randomly assigning 126 patients with early-stage PD to 1 of 3 groups: usual care (wait-listed controls), moderate-intensity exercise (4 days/week at 60%–65% maximal heart rate [HRmax]), or high-intensity exercise (4 days/week at 80%–85% HRmax). At 6-month follow-up, the trial is randomly reassigning usual care participants to a moderate-intensity or high-intensity exercise group for the remaining 6 months. The goals of the Phase II trial are to determine if participants can exercise at moderate and high intensities; to determine if either exercise yields benefits consistent with meaningful clinical change (nonfutility); and to document safety and attrition. The advantage of using a non-futility approach allows us to efficiently determine if moderate- or high-intensity exercise warrants further large-scale investigation in PD.

1. Introduction

Numerous studies have provided preliminary evidence that different types of exercise have positive effects on outcomes such as strength, gait, range of motion, balance, and cardiovascular fitness in patients with early and middle stages of Parkinson disease (PD) [1–12]. In addition, there is growing evidence that exercise, particularly when vigorous, has a neuroprotective effect in animals with PD [1,13]. Although translating high-intensity exercise regimens from animals to humans remains a critical

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next step [14,15], this will require knowledge about the optimal intensity of exercise [16,17] and the feasibility of implementing high-intensity exercise in the human population.

Large, well-designed, randomized controlled trials are needed to establish the impact of endurance exercise to remediate long-term deficits in individuals with PD [17,18]. Phase III multicenter trials are typically large in sample size and costly with respect to resources. Exercise trials can be particularly costly due to the personnel needed for training and supervision of participants to control exposure and ensure safety. As an alternative to launching into a Phase III trial, Schwid and Cutter have indicated that Phase II futility trials appear to be "a clever method of dealing with the trade-off between investment risk and clinical promise" ([21], p. 626). For PD and for other conditions, Phase II futility trials have been used to identify pharmacologic agents that are least likely to warrant further testing in resource-intense Phase III trials [19–23]. The use of a Phase II trial with a futility design allows for testing of an intervention over a shorter period of time and in a smaller number of subjects than does a Phase III trial.

Before we embark on a Phase III trial, we are conducting a rigorous Phase II futility trial to simultaneously establish if either moderate- or high-intensity exercise is feasible and warrants further investigation as a clinically promising intervention for PD. The Study in Parkinson Disease of Exercise SPARX Trial is a multicenter, randomized, controlled, single-blinded study of 2 intensities of endurance exercise. The SPARX trial was dually designed to (1) determine the feasibility of moderate- versus high-intensity endurance exercise in individuals with PD who have not initiated drug therapy and (2) inform the "go, no-go" decision for proceeding to a larger, more resource-intensive trial to determine the efficacy of endurance exercise on the symptomatic improvement of PD. For the Phase II trial, we elected to focus on individuals with de novo PD, defined as patients who are in the earliest stages of PD [24–26] and are naive to therapy or have been receiving therapy for a short period. We made the choice to focus on these individuals not only to minimize the confounding effects of medication and dosage changes on exercise intervention but also to minimize the likelihood that they would have functional limitations that would preclude exercise.

2. Primary research goals

The primary research goals of this exploratory study are to:

1. test whether individuals with de novo PD can adhere to an exercise protocol 4 days a week for 6 months to achieve one of the following randomly assigned levels of exercise intensity: a moderate level with a 60–65% average maximum heart rate (HRmax) or a high level with 80–85% average HRmax;
2. determine if either moderate- or high-intensity endurance exercise warrants further investigation as a therapeutic intervention for motor symptoms in the treatment of de novo PD by conducting a futility trial [21]. The alternate hypothesis is that endurance exercise does not sufficiently differ from usual care to warrant further investigation and is therefore futile;
3. assess the safety of the exercise intervention and the attrition to assist with planning larger exercise trials in persons with de novo PD.

3. Study design

3.1. Overview

One hundred and twenty six patients with de novo PD will be randomly assigned to 3 groups: 1) high-intensity (80–85% HRmax 4 days/week); 2) moderate intensity (60–65% HRmax 4 days/week); and 3) usual care wait-list controls (42 patients

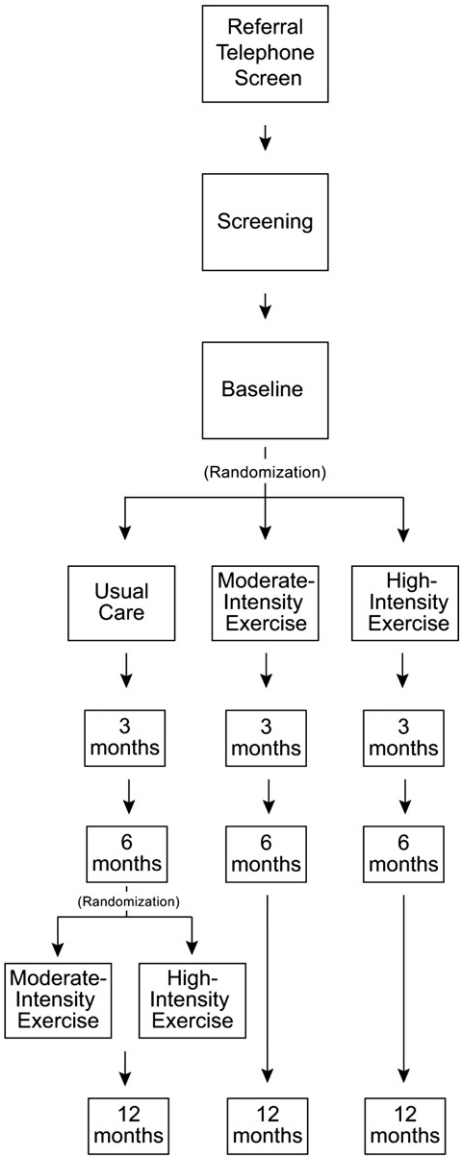

Fig. 1. Design of the Study in Parkinson Disease of Exercise (SPARX) Trial. The moderate-intensity exercise group was assigned to exercise 4 days a week at 60%–65% maximal heart rate (HRmax), and the high-intensity exercise group was assigned to exercise 4 days a week at 80%–85% HRmax. The usual care group was assigned to begin an exercise regimen only after the first 6 months of the trial.