Prevention of Early Postoperative Decline

NCT# 02908464

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PART B
STUDY DESCRIPTION

TITLE OF PROTOCOL	**Prevention of Early Postoperative Decline**
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B1. PURPOSE OF PROTOCOL

Hypothesis:
Patients undergoing cardiac surgery have a high risk of postoperative cognitive decline. Patients who participate in a neurocognitive training program pre- and post-operatively will have a lower incidence of postoperative cognitive decline after cardiac surgery than do controls receiving standard of care.

Specific Aim:
A feasibility study aiming to outline subject interest, adherence to protocol and generation of preliminary data regarding the ability of a neurocognitive training program to reduce the incidence of postoperative cognitive decline after cardiac surgery.

B2. SIGNIFICANCE AND BACKGROUND FOR THE STUDY

Exposure to surgical stress and general anesthesia is associated with the occurrence of postoperative cognitive decline (POCD), with an incidence found to be between 26-40% after the first postoperative week and 15% incidence after three months compared to age matched controls (Moller 1998, Ballard 2012). POCD has been found to be especially prevalent after cardiac surgery, with incidences reported between 30-80% in the first postoperative week and persistent decline found in 24% of patients at six months (Arrowsmith 2000, Newman 2001). A number of surgical, inflammatory, and anesthetic factors are thought to be associated with the increased incidence of POCD in this group of patients, but so far preventative strategies targeting these areas have not been shown to be effective.

With the increasing age and number of comorbid conditions of the cardiac surgical patient in today's health care climate, a new focus for the perioperative team has been optimizing the preoperative condition of the surgical patient through prehabilitation. While promising results have been shown through preoperative physical prehabilitation programs, to date there has been no recommendation for cognitive prehabilitation for cardiac surgical patients to minimize the severity or reduce the incidence of POCD (Debes 2014). Similarly, while the need for physical rehabilitation to recover from the physical stress of cardiac surgery is a well-established and integral aspect of each patient's hospital care and discharge planning, a regimen focused on neurocognitive rehabilitation is not prescribed.

Specific areas of cognition thought to be most affected in the postoperative period include attention, working memory, orientation, and speed of processing (Newman 2001, Hudetz 2009, Saczynski 2012). Lumosity, a neuroscience-based training program, has been shown in various studies to improve subjects' cognitive performance in many of the same cognitive areas (Mayas 2014, Ballesteros 2014, Hardy 2015). We hypothesize that pre- and post-operative training with tailored neuroscience programs provided by Lumosity will result in a decreased incidence of POCD.

B3. DESCRIPTION OF RESEARCH PROTOCOL

A. Study Design – Overview, Methods, Procedures

Research Question:

Does prehabilitation with Lumosity neuroscience training programs reduce the incidence of postoperative cognitive decline after cardiac surgery?

Study Design Overview:

Prospective, randomized, assessor-blinded feasibility trial. Enrolled patients will be randomized into one of two research arms: Neurocognitive training with Lumosity or no training (standard of care control group). Subjects will then be assessed for the development of postoperative cognitive decline and the incidence of delirium in the postoperative period up until postoperative day 7 or discharge, whichever comes first. Subjects will also undergo repeat neurocognitive assessment at 1, 3, and 6 months postoperatively, and complete a Patient Satisfaction Survey at 1-month post-operatively.

Methods:

Preoperative Study Procedures: If deemed a candidate for enrollment, patients will be approached by study personnel to discuss the study in an informed consenting conversation. Once informed consent has been obtained, baseline assessment of cognitive function for both groups will take place at that time and patients with severe baseline cognitive impairment will be excluded. Subjects will then be randomized into either the intervention or control group. Cognitive assessments for the primary outcome in this study will be conducted with the Montreal Cognitive Assessment (MoCA), which has been shown in randomized study to be both highly sensitive and specific for the identification of mild cognitive impairment as compared to the mini mental status exam (Nasreddine 2005).

Creation of Lumosity Accounts: Once enrolled, subjects in the treatment group will be assigned a specific, anonymized user name and email address to use while accessing the Lumosity training program. Subscriptions to the service will be offered free of charge to the subject without the need for identifying information to be shared with the company by virtue of a pre-existing research agreement.

Intervention: Subjects randomized to the treatment group will undergo 30-45 minutes a day total of Lumosity neuroscience training for at least 10 days preoperatively, then for 4 weeks postoperatively. Subjects will be expected to complete at least two 15 minute sessions of Lumosity training per day, but will be limited to a maximum of three sessions per day to minimize long term fatigue in completing the protocol. Subjects randomized to the control group will not participate in Lumosity training.

TREATMENT GROUP:

Lumosity Neurocognitive training program: Subjects will undergo at least two 15-minute training sessions a day utilizing a customized training package provided by Lumosity designed to target the areas of cognition thought to be most affected in the perioperative period based on prior study (Newman, Hudetz, Sacynski). Subjects will be expected to train for at least 10 days preoperatively and then for four weeks postoperatively. Subscription and access to the training programs will be provided free of charge from the company on iPads, provided by the BIDMC Center for Anesthesia Research Excellence group.

Protocol Adherence: Login details, time spent training, and scoring performance statistics will be provided for each user by the Lumosity company via email to the study team. Subject data will be de-identified for this purpose and only subject username and email address will be used to identify the users in each case.

CONTROL GROUP:

Control Condition: Subjects in the control group will be required to refrain from creating a Lumosity account and using their program during the course of the study. They will otherwise prepare for cardiac surgery and undergo perioperative care according to the current standard of care. To date there are no formal recommendations for neurocognitive preparation or rehabilitation in the perioperative cardiac surgical period.

Assessments: A baseline MoCA will take place on the day of informed consent as described above, after enrollment but before randomization. On the day of surgery (or when the subject is admitted for surgery), a repeat MoCA will take place. Cardiac surgery and anesthesia care will proceed in the usual fashion according to current hospital standards, which includes general anesthesia and cardiopulmonary bypass. Patients will be assessed for the presence of POCD and delirium in the postoperative period using two commonly used methodologies: MoCA and the Confusion Assessment Method (CAM). The MoCA will then again be completed on postoperative day (POD) 7 or discharge (whichever comes first), in order to identify trends in POCD. The MoCA will not be used daily during the postoperative period so as to minimize learning effect on test performance.

Delirium assessment will take place every postoperative day until day 7 or discharge (whichever comes first) with the use of the CAM or CAM-ICU assessment tool, which has been used extensively in the hospital setting to identify delirium (Wei 2008). To improve the sensitivity of the delirium assessments, a delirium symptom interview (DSI) will also be performed in conjunction with the CAM/CAM-ICU assessments.

Once the patient is discharged, a telephonic version of the MoCA will take place at 1 month (+/- 7 days), 3 months (+/- 14 days), and 6 months (+/- 14 days) postoperatively. Should a subject return a phone call from the research team outside of the allowable window, the assessments will still occur and the data obtained will be used. A patient satisfaction survey will be administered at the patient's 1-month follow-up which will be entered directly into REDCap. If the patient is unable to complete the survey at the visit, a link directly to the anonymous REDCap survey will be emailed to them.

Data to be Collected: Additionally, to track other important factors related to patient outcome and protocol adherence we may extract clinical data from the medical record such as:

- Anthropometric data (e.g. age, height, weight, race/ethnicity)
- Comorbidities
- Admission type
- Medications
- Respiratory physiological data
- Hemodynamic data (e.g. heart rate, blood pressure)
- Laboratory data
- Complications data
- Hospitalization-related time data (e.g. admitting diagnosis, hospital and ICU length of stay)
- Vital status

Primary Outcome:

Feasibility of utilizing an electronic neurocognitive training program preoperatively, during the hospital period, and postoperatively in a geriatric cardiac surgical population. Feasibility will be assessed by the metrics of consent rates, protocol adherence rates, and patient satisfaction scores.

Secondary Outcomes:

Incidence of postoperative delirium

- Defined according to the Confusion Assessment Method (CAM):
    - Acute onset and fluctuating course
    - Inattention
      AND EITHER
        - Disorganized thinking
      OR
        - Altered Level of consciousness
- Assessed daily until day of hospital discharge
- Assessments will take place using the CAM or CAM-ICU depending on patient condition

Incidence of Postoperative Cognitive Dysfunction (POCD)

- Defined by a decrease of 3 points or greater on the Montreal Cognitive Assessment from baseline
- Assessed on day of hospital discharge, as well as 1 month, 3 months, and 6 months postoperatively
- In person assessments of POCD will be performed using the MoCA, postoperative assessments at 1,3 and 6 months will be conducted with the telephonic MOCA version

Study-Related Encounters:

With a baseline assessment, an assessment on day of surgery, daily assessments on POD 1-6, POD 7 or discharge, and assessments at 1, 3, and 6 months postoperatively, we anticipate a maximum of 12 study related encounters per patient.

Adverse Event Reporting:

This patient population is undergoing high risk surgery and it is expected that they may have a number of unrelated adverse health events during their hospital course. Therefore, we will limit the scope of AE monitoring and reporting to the following:

- All Serious Adverse Events believed to be related to the study procedures
- All non-serious Adverse Events believed to be related to the study procedures

Adverse events will be assessed through the 6-month phone contact.

B. Statistical Considerations

a. Sample Size Justification:

A convenience sample of 45 patients will be chosen in order to assess the feasibility of the Lumosity intervention. A total of 20 enrolled and randomized subjects are needed per group in order to assess the rates of participation, adherence, and drop out associated with the study. To account for patients who may fail the initial MOCA screen, or withdraw prior to randomization, we will add 5 patients to the desired enrollment sample size. Data from these 45 patients will be used to adequately power a larger, likely multicenter trial, based on the treatment effect seen in the feasibility trial.

b. ***Data Analysis:***

Data Analysis: Patients will be prospectively randomized using 1:1 block randomization of equal sizes. Analyses will be conducted using SAS version 9.3 (SAS Institute, Cary, North Carolina) or later. Descriptive statistics of the data will be performed. Continuous data will be represented using mean (± standard deviation) or median (interquartile range) for variables not normally distributed and compared using parametric or non-parametric t-tests as appropriate. Categorical data will be presented using proportions and compared using a chi-square or Fishers Exact test.

Analysis of the Primary Outcome:
The primary outcome of the study is feasibility. Feasibility will be defined in terms of achieving satisfactory recruitment, adherence to protocol, and patient satisfaction. Satisfactory recruitment will be defined as enrollment of greater than 50% of eligible patients during the study period. Adherence to the protocol will be assessed using automated data reports of user activity generated in collaboration with Lumosity. Per protocol patients are expected to complete the intervention twice daily for 10 days preoperatively and 4 weeks postoperatively unless they are incapacitated due to critical illness or intubated. We will define satisfactory adherence as completion of the protocol for greater than 70% of days in which the patient maintains capacity and completes both sessions. Patient satisfaction will be assessed using qualitative data techniques including patient surveys and testimonials

Analysis of Secondary Outcomes:
Differences in the incidence of postoperative delirium and POCD will be presented as proportions and assessed with the use of a chi-square test. Odds ratios and 95% confidence intervals will be reported and interpreted. Although randomization should eliminate baseline confounders, univariate and multivariable logistic regression modeling may be employed to assess the relationship between preoperative luminosity use and both delirium and POCD, adjusting for any differences that may persist between groups.

All data storage and analysis will take place on the BIDMC protected research server. Once collected, patient data will be placed into a REDCap database. Study staff at BIDMC will analyze all data from this project.

C. Subject Selection

Inclusion criteria:

1. Adult age patients (60-90 years) undergoing cardiac surgery
2. Adequate time to implement prehabilitation training intervention: at least 10 days from enrollment
3. Educational attainment of at least a high school level of education or equivalent

Exclusion criteria:

1. Pre-existing history of psychiatric illness as documented in the medical record or divulged in history taking in pre-enrollment patient interview, such as anxiety, depression or bipolar disorder
2. History of cerebrovascular accident or seizure, or a history of dementia, Parkinson's disease, Alzheimer's disease, other forms of cognitive decline
3. Non-English speakers. (Justification: Lumosity tools are provided only in English; cognitive assessment instruments are not validated in a sufficient range of languages, and the research team lacks polylingual capabilities or the financial resources to hire interpreters for the

duration of all proposed assessments)

4. Currently enrolled in another study assessing cognitive ability
5. Significant visual impairment

Drop Out Criteria:

1. After recruitment, enrollment and randomization, patients will be withdrawn from the study if they have a baseline MoCA score of less than 10 as this indicates severe cognitive dysfunction.

**Note: If a patient meets inclusion criteria of being enrolled at least 10 days prior to surgery (adequate time to implement prehabilitation), and surgery is rescheduled to an earlier date by the clinical team, allowing less than 10 days of prehabilitation, the patient will continue in the study and will not be withdrawn.

Patients will not be recruited on the basis of race, ethnicity, or gender. However, it is not clear whether the final study sample will contain a representative spread of the BIDMC racial and gender makeup, as a result of the exclusion of non-English speaking patients. There is no reason to exclude pregnant women from this protocol. However, based on the study plan to recruit patients at highest risk for POCD, we will be recruiting from a patient pool generally exclusive of women of childbearing age largely based on the age requirement.

B4. POSSIBLE BENEFITS

As the proposed study is a feasibility trial, we do not anticipate any specific benefit to be gained by the individual subject, as the intervention in question has never been tested in this arena. However, based on our hypothesis, if the intervention were to result in a lower incidence of post-operative cognitive decline, it can be reasonably inferred that the individuals who did not suffer from POCD would be able to enjoy a higher quality of life, be more functionally independent, and contribute to society in a manner in which they were accustomed to, more so than those who would be cognitively impaired after cardiac surgery. Furthermore, as has been stated in this proposal, to date there are no specific recommendations or interventions prescribed for the prevention of POCD. If the intervention were ultimately successful in a larger study, it could serve as the basis for a new area of perioperative medicine focusing in cognitive training to prevent POCD. Lastly, the insight gained from the interpretation of categorical results from the MoCA assessment could provide further direction into the cognitive areas most affected in the post-operative period.

B5. POSSIBLE RISKS AND ANALYSIS OF RISK/BENEFIT RATIO

As there are no physical interventions planned in this study, we do not anticipate any risk of physical harm to any of the research subjects. The training program has not been used in this arena prior to this study, therefore, there is no published information regarding psychological risk in the perioperative period and any statement of risks would be speculative. Given this, we speculate that there could be psychological or emotional risk to patients in this study if they were to become aware of their cognitive decline more so than they would be if they were not participating in the study. Patients will not be given the scores of their MoCA or CAM assessments, but if they were to become aware of a decline in their performance this could be stressful or disconcerting to the patient. Additional counseling regarding any psychological or emotional distress stemming from this will be provided by the principal investigator at the request of the patient or family. A second potential risk stems from possible dissemination of protected patient information. No identifiable health information will be exchanged between the Lumosity company and the investigators. All PHI will be saved on password protected BIDMC research servers.

B6. RECRUITMENT AND CONSENT PROCEDURES

Recruitment

Eligible patients will be identified by operative scheduling lists, cardiac surgical clinic visit schedules, and pre-admission testing (PAT) clinic visit scheduling lists. If the patient's surgery is to be scheduled at least 10 days in advance from the day of their clinic visit, they will be approached by study staff for inclusion in the proposed study.

Consent

Once a patient is found eligible, he or she will be approached by a member of the study team for informed consent. Informed consent will take place in the preoperative setting, either in cardiac surgery clinic or PAT clinic. All subjects will be consented with curtains drawn or the door closed assuring patient privacy. The subjects will have the opportunity to ask any and all questions, and are free to decline participation at any time. Written informed consent will be obtained and copies provided to the patient and filed in the medical record. The patient may also be provided with an informational handout.

Subject Protection

Although patients of co-investigators may be approached for inclusion in this study, it will be clearly stated that the subjects' decision to participate or refrain from participation in the research study will not affect the performance or outcome of their upcoming surgery. Patients who cannot consent for themselves for reasons of a cognitive disability such as dementia will be excluded from this study.

B7. STUDY LOCATION

Privacy

All study interactions and assessments will take place at BIDMC facilities. For patients being approached for informed consent, if they are uncomfortable answering questions regarding their medical history with someone other than a medical provider than an approved MD participating in the study will be contacted to conduct that portion of the pre-enrollment interview. Interactions and assessments will take place in private clinical settings with curtains/doors closed so as to provide privacy and comfort. Family members will be asked to be present or leave for assessments at the patient's request, so long as they do not interfere with study assessments via provision of answers or coaching. For the follow up telephonic MoCA assessment the patient will be asked if they are comfortable providing answers to the questionnaire at that time. If not, an appropriate time within the same day will be agreed upon between the patient and the study team member conducting the follow up assessment.

Physical Setting

Pre-enrollment screening and informed consent will take place in the BIDMC cardiac surgical or PAT clinics. Assessments will take place in the cardiac surgery or PAT clinics, preoperative holding area and/or patient rooms. Post-operative assessments at 1, 3, and 6 months will take place via telephone. Return of study-related equipment (iPad tablets) will be coordinated with return visits for clinical care.

B8. DATA SECURITY

All files, including those containing PHI, will be stored on a secure research server behind the BIDMC firewall on password protected computers and entered into a REDCap database; paper files will be stored in locked file cabinets/offices at BIDMC. At enrollment, all patients will be given a unique, anonymized study user name and email address that will be used to track their participation in the Lumosity training program. A log of this information will be kept only on BIDMC servers. Limited information will be retained on patients who are prescreened and do not qualify, or who are approached and declined, for the purposes of generating a CONSORT diagram at the conclusion of the trial. Only final analysis produced from the REDCap database will be shared with the Lumosity company.

B9 Multi-Site Studies

Is the BIDMC the coordinating site? ☐ Yes ☒ No

Is the BIDMC PI the lead investigator of the multi-site study? ☐ Yes ☒ No

B10 Dissemination of Research Results

Patients will be thanked for their time throughout the study. There is no plan to share the data at the conclusion of the trial. Because study results are likely to be published a few years after a given subject's participation, it is not feasible to send subjects follow-up with the published results. The study investigators are concerned that mailing the published manuscript and an additional thank-you note years after participation risks violating subject privacy, as mailing addresses are increasingly likely to change with passing time. It is out of the scope of this study to continue tracking mailing addresses after completion of enrollment since this is not a longitudinal study.