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Regenerative Medicine Minnesota
Progress Report
Due: 3/30/2018

Grant Title: Phase I study of delivery of autologous bone marrow derived mononuclear cells to myopathic right ventricle in patients with Ebstein anomaly during surgical intervention

Grant Number: RMM 11215 CT001

Principal Investigator: Kimberly Holst, MD

Project Timeline: 3/1/2016 - 2/28/2020

Progress to Date:
For each specific aim in your proposal, please describe progress and obstacles and/or achievements. Please address any deviations from estimated timelines and limit ***total*** response to 2000 words. Figures and tables are allowed.

We greatly appreciate the no-cost extension approval granted which has extended our timeline to fulfill the aims of our clinical trial. Specific aim updates are outlined below. Overall, we continue to make advancements to the progression of this Phase I Clinical Trial. The most significant change since our NCE application has been the successful approval and implementation of our protocol modification. We have broadened enrollment to include patients up to 30 years of age as well as those who have had previous cardiac surgery if not through a median sternotomy. We're optimistic that this will improve our recruitment as we've recently encountered some hesitation from parents of young children in light of newly released FDA recommendations to avoid anesthetic episodes in children less than 3 years of age.

Additionally, we have improved our Social Media presence through utilization of the RMM sponsored video and internally made videos to improve education about the clinical trial with directed posts on Facebook.

Enrollment Update: Planned enrollment includes 10 subjects into each the Treatment Group and Control Group.

Number of Subjects: Treatment Group / Control Group	
Enrolled to date	7 / 0
Screen Failures	2 / 0
Accrued to date	5 / 0
Completed Study	0 / 0

While there has been a recent lag in subject enrollment we remain optimistic regarding recruitment moving forward this year as our study team has had contact with a number of patients and parents interested in participation.

The **primary aim** is determining safety of BM-MNC injection into the right ventricle with the objective to monitor and document adverse cardiac events including death, sustained/symptomatic ventricular arrhythmias, heart failure, myocardial infarction, infections, and unexpected cardiovascular procedures within 6 months following cell product delivery.

- We have assessed 6-month follow-up results in the initial 4 patients in the cell-therapy group; at this time there were no adverse events and both cell-therapy and delivery method have been evaluated to be a safe adjunct to clinical management.

The **second primary aim** is determining feasibility with objective to establish the percentage of the individuals with collected bone marrow aspirate that meet all release criteria, the percentage of individuals that have cells delivered, and the percentage of individuals completing follow-up, divided into 6-month clinical follow up and 24-month complete follow-up.

- At this time, 5 patients have completed cell-therapy, and have successfully followed up with our research team in accordance with the study protocol.

The **secondary aim** is to determine the efficacy of cell product delivery on improving cardiac function in patients with Ebstein anomaly. Given the small cohort size, the trend of cardiac function will be compared between subjects who received cell product delivery and those who did not and also between subject's preoperative and postoperative cardiac structure and function. Differences will be used to determine power calculations for potential future studies.

- Ongoing.

Please list any of the following that have resulted from the Minnesota Regenerative Medicine grant funding:

Publications and/or manuscripts submitted for publication: "Autologous Bone Marrow Mononuclear Cell Delivery in Children with Ebstein Anomaly: Initial Safety Results" submitted to the Scientific Meeting of the World Society for Pediatric and Congenital Heart Surgery for presentation in July 2018.
Disclosures/patents: None
Grant applications and/or awards: None

Budget Update:
Please see the attached interim financial statement.

Reporting to all Minnesotans:

Briefly and using lay language, please describe your overall progress and how it is significant to the patients in need of regenerative medicine therapies in Minnesota. This will be used on the RMM website to demonstrate how funds are being used to advance the health of all Minnesotans.

The goal of this clinical trial is to study the safety and benefit of cell-based therapy in treatment of congenital heart disease, specifically the use of cells from bone marrow at time of cardiac surgery in Ebstein anomaly. Ebstein anomaly is a form of congenital heart disease, meaning a person was born with this disease, impacting the right side of their heart. Many patients with congenital heart disease have problems with the right side of their heart, the same as those with Ebstein anomaly; because of this the findings of this study will be useful in the treatment of many patients with congenital heart disease.

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There have been very few clinical trials investigating the use of cell-based therapies in congenital heart disease and all of them must go through rigorous assessment and approval by the FDA. This clinical trial has been approved to continue by the FDA along with numerous committees at Mayo Clinic. Given these continuing approvals, we are intent to complete enrollment of patients in both arms of this clinical trial Additional information is available at clinicaltrials.gov, under identifier NCT02914171.

We thank you for your continued support and understanding as we continue to address challenges of patient enrollment.

Sincerely,

Kimberly Holst, MD
Principal Investigator