Regenerative Medicine Minnesota
Progress Report
Due: 3/31/2017

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 - 2/28/2018

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.

The statuses of our aims, which are outlined below, are intimately connected and are principally dependent on patient recruitment. Overall, we have made significant progress in the advancement of this Phase I Clinical Trial in that we have successfully submitted our IND to the FDA, which has been approved under IND16874 on 4/1/16, along with achieving approval through from our institutional IRB on 8/2/16. These approvals did take somewhat longer than anticipated, however we are currently enrolling patients. Enrollment has been limited by patient suitability; the most significant limitations have been the limited age range (6 months to 21 years) and the exclusion of patients with previous surgical intervention.

To address the challenge we have encountered with patient enrollment, we have elected to edit our inclusion and exclusion criteria. The included age will be increased to 30 years of age. The exclusion criteria of 'individuals who have undergone previous cardiac operation' will be updated to 'individuals who have undergone previous sternotomy'. With our original inclusion and exclusion criteria, the number of patients that met criteria for enrollment was five out of 64 patients screened over a ten month period. We anticipate these adjustments will increase the number of patients suitable for recruitment and enrollment in the clinical trial.

To additionally enhance patient enrollment, we have initiated a social media campaign to enhance patient education as related to care of patients with Ebstein anomaly at Mayo Clinic and this clinical trial. IRB approval is pending for a social media article that will be posted on the Ebstein anomaly Facebook page. Additionally, we anticipate the Regenerative Medicine Minnesota video will be a valuable tool in patient education when it is available.

Our challenges with enrollment are currently being addressed and we are confident we will be able to achieve enrollment of 10 patients in each the cell treatment and observational groups. The timeline to achieve complete enrollment will likely be extended from our originally estimated timeline.

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.

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.

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.

Please list any of the following that have resulted from the Minnesota Regenerative Medicine grant funding:
Publications and/or manuscripts submitted for publication: None
Disclosures/patents: None
Grant applications and/or awards: None

Budget Update:
Please see the attached interim financial statement. Due to internal processing delays, this award was made available to the project team for use on 11/15/16. The difference in projected and actual spending over the past year is primarily the result of our altered patient enrollment timeline, as outlined above. The primary investigator and multiple team members have been committed to the advancement and success of this clinical trial, however, we elected to withhold fulfilling compensation with funds from RMM given lack of enrollment. Additionally, Dr. Holst's salary was covered through alternative means over the past funding year and was therefore not deducted from the clinical trial budget in year one. Our budget was primarily determined by patient related costs, and therefore, as patient enrollment is achieved, we anticipate the estimated and actual budgets will balance.

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.

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 proceed by the FDA along with numerous committees at Mayo Clinic. Given these approvals, we are set to enroll patients in the clinical trial now! 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

Joseph Dearani, MD
Co-Investigator

Timothy Nelson, MD PhD
Co-Investigator

Patrick O'Leary, MD
Co-Investigator

Muhammad Yasir Qureshi, MBBS
Co-Investigator

Minnesota Regenerative Medicine Partnership - Phase I Study of Delivery of Autologous Bone Marrow Derived Mononuclear Cells to Myopathic Right Ventricle in Patients with Ebstein Anomaly During Surgical Intervention

Pl: Dr. Kimberly A. Holst, Mayo Clinic

Funding Period: 3/1/2016 - 2/28/2018

Interim Financial Statement: As of 2/28/2017

Account Category	Budget	Actual	Balance Remaining
Salaries and Benefits	$18,161.00	$8,887.00	$9,274.00
Supplies and Services	$8,110.00	$52.00	$8,058.00
Patient Care	$118,107.00	$0.00	$118,107.00
Internal Services	$56,680.00	$0.00	$56,680.00
Total Direct	$201,058.00	$8,939.00	$192,119.00
Indirect	$48,942.00	$5,274.00	$43,668.00
Total Costs	$250,000.00	$14,213.00	$235,787.00

Financial Representative Jennifer Miller 

Role Sr. Program Manager