IMPROVING MITRAL REPAIR FOR FUNCTIONAL MITRAL REGURGITATION (IMPROVE-FMR)

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Sponsor

National Heart, Lung and Blood Institute (NHLBI)

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DEFINITIONS, ACRONYMS, AND ABBREVIATIONS

CCR	Center for Clinical Research
FMR	Functional mitral regurgitation
UMA	Undersizing mitral annuloplasty
IPMS	Inter papillary muscle separation
PMA	Papillary muscle approximation
LV	Left ventricle
MV	Mitral valve
LVEDI	LV End diastolic volume
LVESI	LV End systolic volume index
EF	Ejection fraction
MRF	Mitral regurgitation fraction

1.0 PROTOCOL SUMMARY

Title	Improving mitral repair for functional mitral regurgitation (IMPROVE-FMR)
Precis	Functional mitral regurgitation (FMR) can have an adverse impact on the cardiomyopathic left ventricle, by imposing a chronic low-pressure volume overload. Unrepaired FMR increases the risk of congestive heart failure and death[1, 2]. Undersizing mitral annuloplasty (UMA) is the current gold standard for repair of FMR, but its outcomes are poor[3] with 32.6% of patients presenting with clinically significant recurrent FMR at 1 year after the repair[4], which increases to 58.8% of the patients at 2 years after annuloplasty[5]. Currently, we do not understand why some patients have failure of annuloplasty, while others do not. Lack of mechanistic insights has inhibited an evidence driven approach in optimizing the repairs adequately – resulting in plethora of new sub-valvular techniques, but very few with appropriate scientific justification to be tested in randomized trials. Our team recently performed a retrospective cardiac MRI study in FMR patients and identified that inter-papillary muscle separation (IPMS) is a strong determinant of FMR severity prior to undergoing any repair[6]. Using image-derived computational biomechanical modeling, we reported that when IPMS is elevated, marginal chordal forces restrict parallelization of the leaflet edges and cause higher FMR. We built upon this observation, and performed an ex vivo bench study to demonstrate that IPMS is a strong determinant of repair success as well. In this study, we demonstrated that the MR volume after repair is directly correlated to the pre-operative IPMS[7]. We recently advanced this study further into a chronic swine model, and demonstrated that swine undergoing papillary muscle approximation (PMA) alone or concomitantly with undersizing mitral annuloplasty (UMA), have better valvular function at 3 months after surgery, compared to animals that receive UMA alone. Their valvular kinematics were superior, and so was their ventricular function. In this **observational, prospective, non-randomized study** in humans with FMR, we seek to investigate the following: • **Question 1**: Does pre-operative IPMS correlate with the severity of FMR after UMA at 30 days, 6 months and 12 months. We will study this primary objective by conducting pre-operative MRI and echo in patients receiving UMA, and follow them to one year. Secondly, we will use these images from each patient as input to a computational biomechanical model, which will help demonstrate the chordal forces and stresses before repair, after repair and at the follow-up time points. We will recruit a total of 125 patients to this phase of the study.

	• **Question 2**: Does reducing IPMS with a papillary muscle approximation stitch reduce the FMR severity after UMA, by improving valve geometry and biomechanics. We will conduct a pilot study of 15 patients with this approach and investigate their outcomes at 1 year after the surgery.
Hypothesis	Elevated IPMS is a risk factor for failure of UMA and recurrence of FMR at 12 months the repair. Reducing IPMS with a papillary muscle approximation stitch can reduce FMR recurrence after UMA.
Objectives	(1) Determine if pre-surgery diastolic IPMS, systolic IPMS and (diastolic-systolic) IPMS correlates with the severity of FMR at immediate post-op, 30 days, 6 months, and 12 months post-UMA. (2) Does IPMS reduction with PMA performed concomitantly with UMA, help in reducing the severity of FMR at immediate post-op, 30 days, 6 months, and 12 months after surgery.
Primary Endpoints	The primary endpoint of this study is to investigate if pre-operative inter-papillary muscle separation (diastolic, systolic and diastolic-systolic) correlates with FMR severity at 12 months after surgery with UMA and UMA+PMA.
Secondary Endpoints	**Survival** • All-cause mortality at discharge, 6 months and 1 year **Functional Status and Hospitalizations** • MACE (death, stroke, worsening heart failure (+1 NYHA Class), CHF hospitalization, mitral valve re-intervention at 6 months and 1 year • NYHA classification at 6 months and 1 year • 6-minute walk test at 6 months and 1 year • Readmission rates at 6 months and 1 year **Physiologic** <u>Pre-operative:</u> • MRI - MR severity - Interpapillary muscle dynamics - Left ventricular function - Left ventricular geometry - Left ventricular perfusion and motion defects - Left ventricular scar burden • Echo (transthoracic and transesophageal) - MR severity (ERO and regurgitant fraction)

	- Mitral valve leaflet kinematics - Mitral gradient and stenosis - Left ventricular function - Left ventricular geometry - Left atrial dimensions - Right ventricular size and function - Regional wall motion <u>Intra-operative:</u> • Transesophageal Echo - MR severity (ERO and regurgitant fraction) - Mitral valve leaflet kinematics - LV function <u>Chest closure echo</u>: • Transesophageal Echo - MR severity (ERO and regurgitant fraction) - Mitral valve leaflet kinematics - LV function <u>Discharge:</u> • Transthoracic Echo - MR severity (ERO and regurgitant fraction) - Mitral valve leaflet kinematics - LV function <u>30-days:</u> • Transthoracic Echo - MR severity (ERO and regurgitant fraction) - Mitral valve leaflet kinematics - LV function <u>6 months</u> • Transthoracic Echo - MR severity (ERO and regurgitant fraction) - Mitral valve leaflet kinematics - LV function <u>12 months</u> • Cardiac MRI with contrast or Transesophageal echocardiography • Transthoracic Echo - MR severity (ERO and regurgitant fraction) - Mitral valve leaflet kinematics - LV function
Population	Patients with FMR from either ischemic or non-ischemic cardiomyopathies, referred for surgical or transcatheter mitral valve annuloplasty with or without the need for revascularization. Suitability for mitral annuloplasty is determined by the surgeon, using some or all the criteria described here:

	• Left ventricular end diastolic diameter is less than or equal to 70mm. • Systolic tenting height is less than or equal to 12mm
Inclusion criteria	• Mitral regurgitation of moderate or greater severity, as defined by the guidelines of the American society of echocardiography at the time of the study approval (via a transthoracic echo). • Cardiomyopathy of ischemic or non-ischemic origins, with or without the need for coronary revascularization. • Concomitant right sided valve repair or replacement (i.e. patients requiring concomitant tricuspid procedures). • Age ≥ 18 years • Able to sign informed consent and release of medical information forms, or able to assign a legal representative who can sign on the patient's behalf.
Exclusion criteria	• Any evidence of structural (chordal or leaflet) mitral lesions. • Prior mitral valve repair • Contraindication for cardiopulmonary bypass • Clinical signs of cardiogenic shock at the time of recruitment to the study. • ST segment elevation myocardial infarction within 14 days prior to inclusion in this study. • Congenital heart disease (except PFO or ASD) • Chronic renal insufficiency defined by Creatinine ≥ 3.0 or chronic renal replacement therapy, who are contraindicated for cardiac surgery • Recent history of psychiatric disease that is likely to impair compliance with the study protocol, in the judgement of the investigator • Pregnancy at the time of randomization

Study Procedures	Step 1) Obtain Emory University Institutional Review Board review and protocol approval to begin study. Step 2) Study kick-off meeting, with all investigators and research staff. Study protocol copies to be distributed to each team member. Data coordinators trained to use the study specific redcap database for data entry. Step 3) Recruitment begins. **Patients will be recruited to three registries, with the procedures described as follows:** **Registry # 1: Prospectively Identified Patients that will Receive Surgery after Recruitment and Consented to Participate in the Study** Step 4) Subjects are screened based upon medical records, external echo examinations, echo exams performed in the Emory cardiology clinics or cath labs, inclusion and exclusion criteria. Step5) Screened patients are consented and request for release of medical information is signed. Step6) Consented patients undergo battery of baseline tests that are standard of care, including transthoracic echo, transesophageal echo, and cardiac MRI. If some patients have already completed baseline tests as part of their standard of care, and are identified after these are completed, we will consent them at this stage. Step7) Patients undergo surgery, with pre-operative echo and closed chest echo. Step8) Blood draws and echocardiography performed at discharge and 30-days. Step9) Patients return for visits at 6 months and 1 year to undergo repeat of tests. Step10) Patients exit study after the 1st year. If extended follow-up is determined to be necessary, patients will be re-consented at the 1-year visit. **Registry # 2: Retrospectively identified patients, who already underwent the standard of care surgery, and were identified after the procedure is completed, and are suitable for recruitment to the study for their post-operative research**

	Rationale: The decision to perform mitral valve surgery could be made during the surgery by the surgeon, and these patients would be suitable for this study, but would not be consented prior to their surgery. Thus, in this registry, we will identify such patients for recruitment into this study, as their first research point isn't until 6 months after their surgery. Step 1) Charts will be screened for patients who underwent surgery for the lesion of interest at Emory, who would otherwise be eligible for this study but were not recruited as it was not known if they will need mitral valve surgery. Step 2) Patients who are still within 6 months (± 1 month) after the date of their surgery will be contacted after surgery and the study objective will be explained, verbal consent will be obtained and the date to visit Emory will be provided. Step 3) Written consent will be obtained at their 6 month visit, and steps 9 and 10 described in registry # 1 will be performed. **Registry # 3: Retrospectively identified patients, who already underwent the standard of care surgery, and were identified after the procedure is completed, and are suitable for recruitment to the study for their post-operative research.** **Rationale:** Historical review of patients between dates 1/1/2004 to present who have underwent mitral valve surgery who were not previously identified in the study. These patients have not been consented prior to their surgery. The purpose is to increase the study sample size in order to gain statistical power for outcome analysis. Step 1) Charts will be screened for patients who underwent surgery between 1/1/2004 to present for the lesion of interest at Emory, who would otherwise be eligible for this study but were not recruited as it was not known if they will need mitral valve surgery or were not recruited as they may have received the surgery prior to study start date.
Sample size	140 subjects in total at Emory University. **Group 1**: 125 patients to receive UMA and followed to 12 months, with interim imaging. **Group 2**: 15 patients to receive UMA with PMA and followed to 12 months, with interim imaging.

	It is expected that we will recruit ~25 patients per year. **Group 3:** patients' medical charts will be queried between 2004 – present, number of subject charts are undetermined/unknown.
Risk-benefit determination	Neither UMA nor PMA are experimental procedures, thus the risk from the procedures itself is considered minimal[8, 9]. Surgeons at our institution have experience with both procedures in humans, albeit with more extensive experience with undersizing mitral annuloplasty and recent preliminary experience with papillary muscle approximation. Proposed pre-operative and post-operative echocardiography and MRI are non-invasive, and thus the risk from these procedures is minimal as well. The data obtained from such imaging may not directly impact the patients care, however if any recurrence of FMR or deterioration in cardiac function is observed from the study imaging, the investigative team will inform the patient to consult their cardiologist. Thus, the patients stand to gain some benefit from participating in the study. Overall, our study team determined that benefits significantly outweigh the risks to the patients participating in this study.
Number of sites enrolling participants	Emory University Hospital/Emory University Midtown Hospital/Emory St. Joseph's Hospital.
Study duration	20 years.
Participant duration	1 year from the time of surgery.

2.0 OBJECTIVE

The primary objective of this protocol is to investigate if pre-operative inter-papillary muscle separation (IPMS) is predictive of FMR severity at 12 months after undersizing mitral annuloplasty (UMA) to repair functional mitral regurgitation (FMR). Furthermore, whether a cut-off value of pre-operative inter-papillary muscle separation can be established to predict patients who might have failure of UMA.

The secondary objective of this protocol is to investigate if adding papillary muscle approximation (PMA) to UMA is an effective technique in reducing recurrence of FMR at 12 months' post-procedure.

The third objective is to use computational modeling to define the impact that IPMS has on chordal force imbalance, to define the mechanistic basis for repair failure. MRI and echo images from the patients will be used to accomplish this objective.

3.0 BACKGROUND

Functional mitral regurgitation (FMR) is a frequently diagnosed mitral valve lesion in patients surviving cardiomyopathies of ischemic and non-ischemic origins[10-18]. Volume overload from FMR increases the risk of congestive heart failure and death. Pharmacological management of these patients has been shown to be ineffective, and thus timely repair of FMR is considered to benefit the patient and preserve their cardiac function.

Undersizing mitral annuloplasty (UMA) is the current standard of care to repair FMR, which involves placing a metallic ring onto the mitral annulus, to reduce its dimensions[19]. This procedure can be performing using open heart surgical techniques or with transcatheter mitral valve techniques. Though UMA is considered effective, there is increasing evidence that FMR persists or recurs after the procedure. At 12 months, ~36% of the patients present with recurrence FMR, which increases to 58% at 24 months[4]. The mechanisms driving failure of UMA are unknown, and a metric for pre-operative stratification of patients to benefit from UMA is necessary.

Our group recently reported that in patients presenting with FMR, inter-papillary muscle separation (IPMS) has a strong correlation with the pre-operative severity of the regurgitation[6]. Using cardiac MRI imaging, we demonstrated that IPMS directly impacted the extent of leaflet tethering and mitral regurgitation, independent of the left ventricular size or volume. We used biomechanical modeling to demonstrate that elevated IPMS increases the forces in the marginal chordae, resulting in improper leaflet closure.

In a more recent study in a bench-top ex-vivo model, we demonstrated that IPMS can also have an impact on mitral valve closure after undersizing mitral annuloplasty (UMA). Specifically, we demonstrate that when the IPMS is elevated, UMA results in a highly unphysiological leaflet geometry that results in persistent FMR despite the repair[7]. In a similar study in swine, we demonstrated that such an unphysiological leaflet configuration after UMA can be improved with papillary muscle approximation (PMA)[20].

In this observational, prospective, non-randomized clinical study, we seek to test the hypothesis that elevated pre-operative inter-papillary muscle separation (IPMS) is a risk factor for recurrence

of FMR after annuloplasty. Since high or low are subjective terms, we seek to recruit 125 patients undergoing undersizing mitral annuloplasty (UMA) at our institution and measure their inter-papillary muscle separation before and after the procedure, and study their impact on 12 month outcomes of the repair. We will perform statistical analysis to determine a cut-off value for IPMS that can stratify patients at risk for UMA failure.

Using the patient specific imaging that we obtain from the 125 patients, we will perform comprehensive biomechanical computational modeling to demonstrate and validate that patients below the cut-off value of IPMS have better mitral valve force distribution, vs. those above the cut-off value of IPMS having poor mitral valve force distribution. This data will help validate the cut-off value as a viable technique to stratify patients for UMA.

In the final step of this study, we will demonstrate that those patients with higher IPMS and at risk of UMA failure, may benefit from a concomitant papillary muscle approximation technique. We will recruit 15 patients to a pilot study, in whom IPMS is above the cut off value, and perform papillary muscle approximation (PMS) along with undersizing mitral annuloplasty (UMA). We will investigate the effect of this combination approach on the outcomes at 6 months and 12 months.

4.0 CLINICAL AND SCIENTIFIC JUSTIFICATION

Failure of undersizing mitral annuloplasty (UMA) in patients with FMR is now an established fact. High rates of FMR recurrence after UMA have been reported in several studies, but a mechanistic basis for such failure is lacking. Due to the high rates of repair failure, these patients are receiving a mitral valve replacement (MVR), which is known to have poor durability and higher mortality. Thus, the clinical justification to understand the mechanisms underlying UMA failure is solid. The knowledge gained from this study may not directly impact these patients, but is expected to improve the treatment options available to other patients in the future.

The scientific justification for studying inter-papillary muscle separation (IPMS) as a determinant of UMA failure, stems from our previous published study. In 2014, we reported that elevated IPMS correlated with higher severity of FMR in humans. In a subsequent study in a bench model, we reported that elevated IPMS has a direct impact on valve function after UMA. Based on these two studies, we developed the hypothesis that a cut-off value for IPMS exists, which can determine who patients could have a durable repair with UMA, and which patients may require additional procedures. Based on this information, for those with higher IPMS we are proposing that papillary muscle approximation (PMA) may be a useful technique to reduce their IPMS and improve their suitability for UMA.

5.0 TREATMENT OPTIONS

Patients recruited to this study, are determined by their cardiologists to be suitable for correction of their FMR to improve their health. A transthoracic echo has been performed on them, which

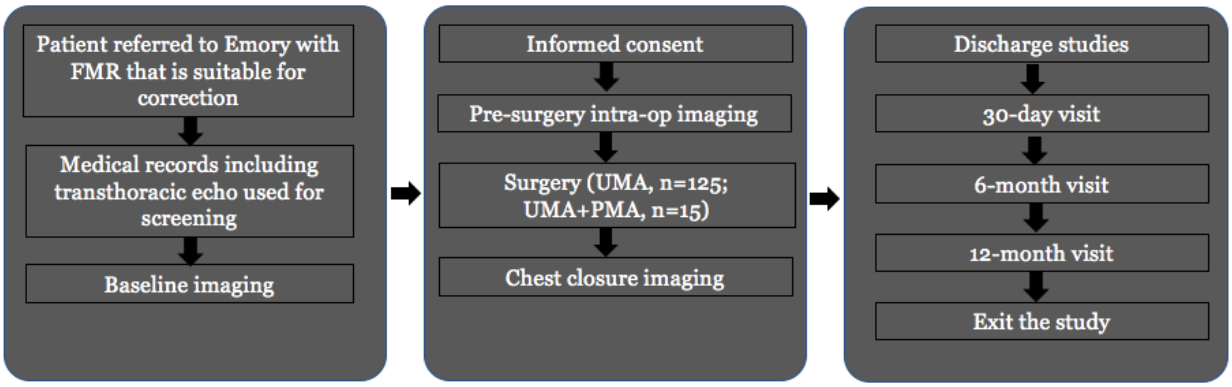
depicts moderate or greater severity of FMR, and thus they were referred to us for intervention. The patients may receive mitral valve repair or mitral valve replacement, depending on their choice along with advice from the physician team. Risks and benefits of both the treatment options will be explained to the patient. If mitral valve repair is planned in these patients, they will be recruited to this study. If mitral valve replacement is planned, they will not be recruited to this study. If mitral valve repair is planned, but intra-procedurally the physician decides that mitral valve replacement is more apt, they will continue in the study. If mitral valve replacement is planned, but intra-procedurally the physician decides that mitral valve repair is more apt, they will continue in the study.

6.0 STRATEGIES FOR RECRUITMENT

Trial recruitment will be handled by the clinical research unit of the division of cardiothoracic surgery at Emory University. Patients will be referred to this trial from cardiology groups within Emory University, and from external cardiologists that do not have any affiliation with Emory University.

7.0 STUDY DESIGN

7.1 Schematic of study design



7.2 Overview of study design

This is an observational, prospective, non-randomized, clinical study to investigate the mechanistic basis for failure of undersizing mitral annuloplasty (UMA) and the efficacy of adding papillary muscle approximation (PMA) as an additional technique to UMA to improve its outcome.

Screening: Patients with FMR will be identified in cardiology and cardiothoracic surgery clinics at Emory Hospital, Emory St. Joseph's Hospital and Emory Midtown, and outside referral centers that refer patients to the cardiac surgery program at Emory. Existing patient medical records, including their imaging reports, will be used to identify patients with FMR. Through the duration

of this study, we will actively inform and educate our internal and external referral cardiology groups about this study, so they can refer patients to our trial. Patient medical records and imaging examinations will be used to screen for patients. Coronary angiograms that are less than 6 months old will be used to assess the cardiomyopathic process.

Informed consent: Patients that successfully clear the screening process will be approached, and provided a thorough explanation of the study purpose, procedures, risk/benefits, alternatives and follow-up schedule. If patient volunteers to participate in the study, he/she will be asked to sign one copy of an informed consent which will be copied. The original will be included in the study record, a copy will be given to the patient, and a copy scanned and uploaded to EeMR by OCR. In some cases, it is possible that some patients may undergo all the standard of care examinations before being able to be consented for the study. In such case, the patients will be consented prior to surgery, explaining to them that the study team will use their medical records and imaging information conducted prior to the consent in this study.

Release of medical information form: The patient will also sign the release of medical information form or equivalent that authorizes release of medical records, to the study investigators and sponsors.

Study recruitment: All consented patients will undergo the following standard-of-care procedures to determine their eligibility to be recruited to this study. The study team will generate a unique identification code that will identify the patient throughout the course of the study.

Following studies will be performed as standard of care procedures for patients receiving mitral valve repair, whether part of this study or not:

- Functional status assessment
- Transthoracic echocardiogram (if >6 months)
- Transesophageal echocardiogram (may use the baseline TEE in OR)
- Coronary angiogram (if >6 months)
- Medical history
- New York Heart Association Class
- Angina Class – Canadian Cardiovascular Society Classification
- Medications
- Physical examination
- Quality of life (study purposes only)
- Laboratory assessment (study purposes only)
- Cardiac MRI with gadolinium enhancement

Inclusion/Exclusion criteria:

Inclusion criteria:

- Mitral regurgitation of moderate or greater severity, as defined by the guidelines of the American society of echocardiography (via a transthoracic echo).
- Cardiomyopathy of ischemic or non-ischemic origins, with or without the need for coronary revascularization.
- Concomitant right sided valve repair or replacement (i.e. patients requiring concomitant tricuspid procedures).
- Age ≥ 18 years
- Able to sign informed consent and release of medical information forms

Exclusion criteria

- Any evidence of structural (chordal or leaflet) mitral lesions.
- Prior mitral valve repair
- Contraindication for cardiopulmonary bypass
- Clinical signs of cardiogenic shock at the time of randomization
- ST segment elevation myocardial infarction within 14 days prior to inclusion in this study.
- Congenital heart disease (except PFO or ASD)
- Chronic renal insufficiency defined by Creatinine ≥ 3.0 or chronic renal replacement therapy, who are contraindicated for cardiac surgery
- Recent history of psychiatric disease that is likely to impair compliance with the study protocol, in the judgement of the investigator
- Pregnancy at the time of randomization

Patients will be recruited to two registries, with the procedures described as follows:

Registry # 1: Prospectively Identified Patients that will Receive Surgery after Recruitment and Consented to Participate in the Study

Subjects are screened based upon medical records, external echo examinations, echo exams performed in the Emory cardiology clinics or cath labs, inclusion and exclusion criteria. Screened patients are consented and request for release of medical information is signed. Consented patients undergo battery of baseline tests that are standard of care, including transthoracic echo, transesophageal echo, and cardiac MRI. If some patients have already completed baseline tests as part of their standard of care, and are identified after these are completed, we will consent them at this stage. Patients undergo surgery, with pre-operative echo and closed chest echo. Blood draws and echocardiography will be performed at discharge and 30-days. Patients return for visits at 6 months and 1 year to undergo repeat of tests. Patients exit study after the 1st year.

If extended follow-up is determined to be necessary, patients will be re-consented at the 1-year visit.

Registry # 2: Retrospectively identified patients, who already underwent the standard of care surgery, and were identified after the procedure is completed, and are suitable for recruitment to the study for their post-operative research

Rationale: The decision to perform mitral valve surgery could be made during the surgery by the surgeon, and these patients would be suitable for this study, but would not be consented prior to their surgery. Thus, in this registry, we will identify such patients for recruitment into this study, as their first research point isn't until 6 months after their surgery.

Charts will be screened for patients who underwent surgery for the lesion of interest at Emory, who would otherwise be eligible for this study but were not recruited as it was not known if they will need mitral valve surgery. Patients who are still within 6 months (± 1 month) after the date of their surgery will be contacted via telephone, and the study objective will be explained, verbal consent will be obtained and the date to visit Emory will be provided. Written consent will be obtained at their 6 month visit, and steps 9 and 10 described in registry # 1 will be performed.

Registry # 3: Retrospectively identified patients, who already underwent the standard of care surgery, and were identified after the procedure is completed, and are suitable for recruitment to the study for their post-operative research.

Rationale: Historical review of patients between dates 1/1/2004 to present who have underwent mitral valve surgery who were not previously identified in the study. These patients have not been consented prior to their surgery. The purpose is to increase the study sample size in order to gain statistical power for outcome analysis.

Medical charts will be screened for patients who underwent surgery between 1/1/2004 to present for the lesion of interest at Emory, who would otherwise be eligible for this study but were not recruited as it was not known if they will need mitral valve surgery or were not recruited as they may have received the surgery prior to study start date.

Study assignment: 140 patients will be recruited in total, 1) n=125 to undersizing mitral annuloplasty (UMA) and 2) n=15 to undersizing mitral annuloplasty with papillary muscle approximation (UMA+PMA). Selection will be in a non-randomized manner. Under no circumstances will more than the proposed number of patients be recruited to either groups, without prior approval from the institutional IRB and the study sponsor.

Surgical procedures:
Intra-operative echo 1: On the day of the surgery, after the patients are sedated, intubated and anesthetized, the cardiac anesthesiologist will perform a standard of care transesophageal echocardiogram.

Surgical procedures:
Undersizing mitral annuloplasty (Figure A): Patients undergoing this procedure will receive a commercially available annuloplasty ring of the surgeon's choice. Sutures are placed around the mitral annulus, and the metallic ring is then implanted onto the mitral annulus to reduce it in size.

Undersizing mitral annuloplasty with papillary muscle approximation (Figure B): Patients receiving this procedure will undergo undersizing mitral annuloplasty in a manner that is identical to the procedure outlined above. In addition to the ring implantation, one or two 4-0 pledgeted sutures are used to draw the two papillary muscle tips together to reduce the IPMS.

After the procedure is complete, the patients are revived from cardiopulmonary bypass and hemodynamic stability is established.

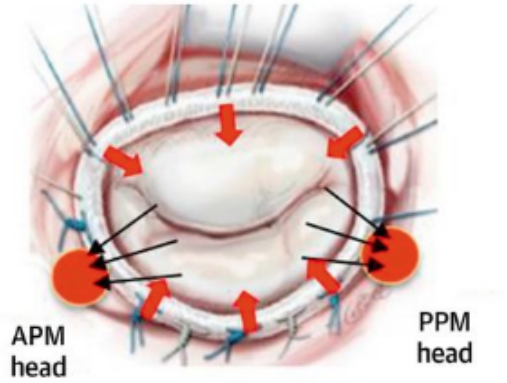


Figure A: Undersizing mitral annuloplasty

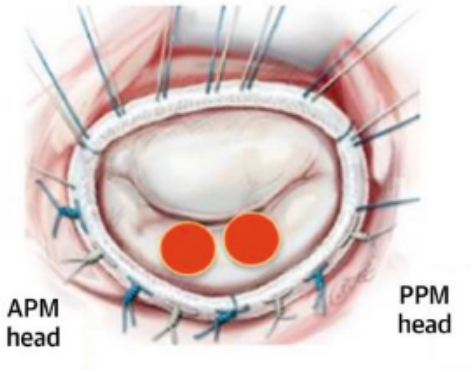


Figure B: Papillary muscle approximation

Post-chest closure echo: Just prior to moving the patient out of the operating room, a repeat intra-operative standard-of-care echocardiogram will be performed to assess the valve function. After both procedures, the patients are revived from surgery and their post-operative care will follow established and standard of care protocols.

Follow-up time points and examinations:
Discharge: Following examinations will be performed before discharge:

- Transthoracic echocardiography

- Blood draw

30-day (+/- 7 days): Following examinations will be performed at 30-days :

- Blood draw
- Transthoracic echocardiography

6 months post-surgery (+/- 30 days): Following examinations will be performed at discharge at 6 months post-surgery

- Transthoracic echocardiography
- Blood draw
- Quality of life questionnaire
- HF questionnaire
- 6 minute walk test

12 months post-surgery (+/- 90 days): Following examinations will be performed at discharge at 6 months post-surgery

- Transthoracic echocardiography
- Cardiac MRI with contrast or transesophageal echo (whichever is possible)
- Blood draw
- QoL questionnaire
- Heart failure questionnaire
- 6MWT

Computational biomechanical modeling: Echocardiographic images, immediately after acquisition will be transferred to the core database established by the PI's laboratory. These images obtained from the patients at the different timepoints will be used for computational biomechanical modeling. The 3D echocardiographic images will be segmented and a mathematical mesh will be developed. Idealized material properties will be assigned to the mesh geometry, and the strain and stress distribution on the leaflets will be quantified under different loading conditions.

8.0 TIMEFRAME OF MEASUREMENTS AND DATA COLLECTION

	TTE	TEE	MRI	QOLq	HFq	6MWT	Blood
Screening	x						
Pre-op	x	X*	X*	0	0	0	0
Intra-op		x					
Chest closure		x					
Discharge	x						0
30 days	x						0

6 months	**0**			**0**	**0**	**0**	**0**
12 months	**0**	**0***	**0***	**0**	**0**	**0**	**0**

x: indicates current standard of care
0: indicates non-standard of care, paid by the study
***: indicates that both procedures could be performed, or only one of them, depending on what is practically possible and what the patient agrees to undergo.**

TTE: trans-thoracic echo
TEE: trans-esophageal echo
MRI: magnetic resonance imaging
QOLq: quality of life questionnaire
HFq: heart failure questionnaire
6MWT: 6-minute walk test
Blood: blood collection for laboratory studies

9.0 DEFINITIONS AND MEASUREMENT OF ENDPOINTS

Primary Endpoints:	The primary endpoint of this study is to investigate if pre-operative inter-papillary muscle separation (diastolic, systolic and diastolic-systolic) correlates with FMR severity at 12 months after surgery with UMA and UMA+PMA.
Secondary Endpoints:	**Survival** • All-cause mortality at discharge, 6 months and 1 year **Functional Status and Hospitalizations** • **MACE** MACE is defined as a non-weighted composite score comprised of the following: - Death - Stroke - Worsening heart failure (+1 NYHA class) - CHF hospitalization - Mitral valve re-intervention • **NYHA classification** Functional status will be assessed by the NYHA classification scale. (**Appendix 1**) • **6-minute walk test** Functional status will also be measured by a 6-minute walk test, which assesses the distance walked (in feet) during the pre-specified time period. The test will be administered by a trained study coordinator. (**Appendix 2**) • **Readmission rates**

	Readmission rate will be calculated for any cause within the first 30 days and for all cause, cardiovascular and heart failure after 30 days following surgery. Classification of readmission as heart failure related requires at least 2 out of the following signs and symptoms of acute decompensated heart failure: - Dyspnea felt related to HF - Treatment with intravenous diuretic, vasodilator or inotropic therapy - X ray evidence of pulmonary edema or pulmonary vascular congestion - Rales on physical exam - PCWP or LVEDP > 18mm Hg All readmissions will be classified by the investigator and adjudicated by the event adjudication committee. **Physiologic** • **Echocardiographic parameters** *Presence and severity of mitral regurgitation* will be assessed by measuring the effective regurgitant orifice area (EROA) by both the proximal isovelocity surface area and the quantitative flow methods. If it is not possible to assess MR using these techniques, MR will be assessed by tracing the jet area and normalizing by the left atrial area. *Mitral valve apparatus* and quantification of valve area will be assessed by evaluating annular shape and motion, tethering angle and tenting area, papillary muscle position and separation, and calculation of mean trans-mitral stenotic gradient by mitral inflow continuous wave Doppler. *LV size, geometry and function* will be assessed by the following measures: LV dimensions, ejection fraction (biplane Simpson's rule), LV end-systolic volume index using the biplane volumetric method, LV mass, LV sphericity, radial strain, and twist. *RV size and function* will be assessed by the following measures: tricuspid annular plane systolic excursion (TAPSE), peak systolic velocity, diastolic E and A velocity (by tissue doppler), and fractional area change. *Left atrial dimension and volume* will be assessed.

	Intracardiac pressures and hemodynamics, including pulmonary artery pressures and pulmonary capillary wedge pressure will be assessed by Doppler flow studies. *Regional Wall Motion* (LV function and viability assessment) will be assessed at baseline and again at one year following surgery. *Inter-papillary muscle separation* (IPMS) is measured as the distance between the centers of the antero-lateral papillary muscle and postero-medial papillary muscle in a short axis echo plane. IPMS will be measured at three locations: papillary muscle tips, mid-body and base. IPMS will be measured in each frame of the cine loop, optimized to obtain at least 20 frames per heart beat. IPMS is reported in diastole, systole and differences between diastole and systole. • **Cardiac MRI parameters** Late-Gadolinium enhanced cardiac MRI will be performed on all patients pre-operatively. Standard protocols will be used to obtain 2 and 4 chamber gated images of cardiac chambers. *Presence and severity of mitral regurgitation* will be measured as (total stroke volume (EDV-ESV)) – (aortic forward ejection (measured using flow encoded MRI imaging at the aortic valve annulus)). Measurements will be obtained using flow encoded MRI at the mitral annular plane as well. *LV size, geometry and function* will be assessed by the following measures: LV dimensions, ejection fraction (segmenting LV from short axis and rotated long axis images), LV end-systolic volume index using the biplane volumetric method, LV mass, LV sphericity, strain, and twist. *Regional Wall Motion* (LV function and viability assessment) will be assessed at baseline and again at one year following surgery. *Inter-papillary muscle separation* (IPMS) is measured as the distance between the centers of the antero-lateral papillary muscle and postero-medial papillary muscle in a short axis echo plane. IPMS will be measured at three locations: papillary muscle tips, mid-body and base. IPMS will be measured in each frame of the cine loop, optimized to obtain at least 20 frames per heart beat. IPMS is reported in diastole, systole and differences between diastole and systole.

	Scar burden and localization will be measured using lade Gd enhancement in the myocardium, measured using Otsu's method. • **Quality of life questionnaires** The change in quality of life (QOL) from baseline will be measured, using the disease specific Minnesota Living with Heart Failure (MLHF) score, Duke Activity Status Index Questionnaire and EuroQol 5-D measures of health state preference from the individual and societal perspective. The Minnesota Living with Heart Failure Questionnaire is a disease specific instrument that measures the perception of the physical, psychological and social effects of heart failure (HF) and HF treatment on the patient. The Duke Activity Status Index measures a patient's functional capacity. It can be used to get a rough estimate of a patient's peak oxygen uptake. The EuroQoL 5-D is a standardized instrument for measuring health-related quality of life. This questionnaire provides a simple descriptive profile that consists of 5 dimensions. The 5 domains are anxiety/depression, pain/discomfort, usual activities, self-care, and mobility. The instrument also has a self-assessment of health status. (**Appendix 3**). • **Laboratory Tests** Blood collection will be performed using standard phlebotomy techniques at the time of the patients visit ±7 days of the targeted date. The study nurse drawing the blood will label the tube with the patient's specific code. The blood is then centrifuged to separate plasma and serum, and the plasma and serum are snap frozen. The frozen sample is then shipped to the core laboratory designated by the PI. The core laboratory will record every sample received from the study using an electronic tracking system, and the sample will be stored at -80C. When adequate number of samples (60-80) are acquired, multiple biomarker arrays will be run to measure the quantity of the biomarkers in the sample. Some examples of biomarkers include, Brain natriuretic peptide (BNP), MMPs, TIMPs and catecholamine's etc. Samples remaining after all the tests are performed will be banked.

10.0 DATA MANAGEMENT

A secure redcap database (www.redcap.emory.edu) will be used to maintain enrollment records and patient information. Study personnel requiring access will have their own login and password. Access to clinical study information will be based on individual roles and responsibilities. The application provides hierarchical user permission for data entry, viewing and reporting options. Imaging data will be acquired and viewable to investigators on hospital application.

Confidentiality of patient data: By removing the patient information and blinding the datasets, the risk of loss of patient data confidentiality is reduced. Through the entire study, secure networks and databases will be used to manage the data, reducing the risk of any confidentiality breaches. However, there is always a risk of cyber-attacks that may compromise confidential data, and if this study is impacted by such a cyber-attack, the patients and the sponsor will be intimated within 10 days of its discovery.

Quality assurance: Quality control of all data will occur automatically, based upon the rules described for each field in the software. Whenever a patient is registered into the system, and a specific field is not entered, the software will prompt for a descriptive reason for not entering the data and the principal investigator will receive a form describing the instance. The investigative team will then explore the event appropriately, and make a note of the reasons or rectify accordingly.

Monitoring: The research study coordinator will perform a data audit at 6 month intervals and present the report to the principal investigator. Source files obtained from the patient records will be matched against the data entered into the study database. A minimum of patient last name, first name, date of birth, hospital accession number, sex, informed consent, eligibility criteria, date of enrollment, serious and protocol defined adverse events, mortality, heart failure class, 6 minute walk test and QoL questionnaire will be verified. These data will be 100% source verified. All other data collected will be monitored for data completeness and accuracy.

Regulatory audit: A regulatory audit will be performed at time intervals that the IRB deems necessary for this study protocol. The Principal Investigator and coordinators will be available as necessary.

11.0 ANALYSIS PLAN

General design issues: This is an observational, prospective, non-randomized, single center, multiple phase study. Enrolled patients will have clinically significant FMR with either ischemic or non-ischemic cardiomyopathies. 50 patients are recruited to phase 1 (all 50 receiving undersizing mitral annuloplasty), and 90 patients to phase 2 (75 receiving undersizing mitral annuloplasty and 15 receiving undersizing mitral annuloplasty and papillary muscle approximation). In patients

receiving undersizing mitral annuloplasty, the same rigid annuloplasty ring will be used as consistently as possible, and up to two sizes of downsizing will be performed as consistently as possible. In some patients recruited to the study, the surgeon may decide to switch to mitral valve replacement, or may perform a repair and deem it to be a failure and then switch to mitral valve replacement. In either case, the patient will continue to be part of the study, but with follow-up performed only at 12 months.

Sample size estimation and statistical analysis plan: The primary objective of this study is to determine the correlation between pre-operative inter-papillary muscle separation and the 6 month and 12 month post-operative FMR grade after undersizing mitral annuloplasty. Pre-operative inter-papillary muscle separation will be measured and is a continuous variable, while the recurrence of FMR will be deemed binary (1: if MR greater than or equal to 2+ severity observed at 12 months; 0: if MR less than or equal to 2+ severity observed at 12 months). An ROC curve analysis will be used to determine the inflection point of inter-papillary muscle separation at which FMR will recur at 12 months after annuloplasty. Sample sizes are based on previously published data, and on ensuring the ability to detect with high probability, a clinically meaningful presumed benefit for patients undergoing mitral valve repair.

Recruitment to the papillary muscle approximation arm is not based on power analysis as it is only a pilot study.

12.0 ADVERSE EVENT REPORTING

Considering the observational nature of this study, and lack of any experimental procedures, adverse event reporting will be limited only to those events that may occur from the specific non-standard of care lab procedures that are performed at 6 and 12 month visits. Adverse events at these 6 and 12 month visits are described here.

11.1 Definitions

Adverse events: An adverse event is any undesirable clinical occurrence in a study patient, that is related to a study intervention that is non-standard of care. Any condition that was recorded as pre-existing or that is associated with standard of care procedures that the patient has consented to is not an AE unless there is a change in the nature, severity or degree of the condition.

Serious Adverse Events (SAE): Serious adverse events are defined by FDA regulation as any experience that results in a fatality or is life threatening; results in significant or persistent disability; requires or prolongs a hospitalization; or represents other significant hazards or potentially serious harm to research subjects or others, in the opinion of the investigators. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical

intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization.

Unanticipated Serious Adverse Event: An unanticipated (unexpected) serious adverse event is any serious adverse event that is not protocol-defined or documented in the patient consent form. Expedited reporting is required for serious adverse events that are unexpected.

Event Recording: The following adverse events will be captured throughout the period of trial participation:

- Protocol-defined (as described below)
- Serious unanticipated events (serious "Other" adverse events)

Causality: The investigator will assess the relationship of an adverse event to the proposed non-standard of care lab assessments and imaging studies. Causality will be defined as follows:

Probable

Adverse events that, after careful medical evaluation, are considered with a high degree of certainty to be related to the proposed follow-up imaging and blood draw studies that are non standard of care.

The following characteristics will apply:

- A reasonable temporal relationship exists between the event and the procedure, and
- The event is a known reaction to the non-standard of care procedure, which can be explained by an alternative etiology commonly occurring in the population/individual, or
- The event is not a known reaction to the proposed non-standard of care procedure but cannot be reasonably explained by an alternative etiology.

Possible

Adverse events that, after careful medical evaluation, do not meet the criteria for a probable relationship to the non-standard of care procedure, but for which a connection cannot be ruled out with certainty. The following characteristics will apply:

- The event occurs after non-standard of care procedure, and
- The event is not a known reaction to non-standard of care procedure, but cannot be explained by a commonly occurring alternative etiology

Unlikely

Adverse events that, after careful medical evaluation, do not meet the criteria for a possible or probable relationship to non-standard of care procedure for which a connection is unlikely. The following characteristics will apply:

- The event does not follow a reasonable temporal sequence from administration of the non-standard of care procedure, or
- May have been produced by environmental factors, and there is no apparent pattern of response to the non-standard of care procedure.

Reporting of Serious Adverse Events

All investigators conducting the clinical study supported by the NHLBI must report both expected (protocol-defined) and unexpected serious adverse events. All serious adverse events must be reported as dictated by the specific IRB policy. Deaths unrelated to study participation will be reported to the IRB at the time of continuing review. Deaths related to study participation and associated with the non-standard of care procedures will be promptly reported to the IRB. The PI will notify the NHLBI program officer of any unexpected serious adverse events via e-mail within 24 hours of receipt of the event.

Specific Adverse Event Definitions

Bleeding: A bleeding event is defined by any one of the following:

- Transfusion of > 10 unit's RBC within the first 24 hours following surgery
- Death due to hemorrhage
- Re-operation for hemorrhage or tamponade

NOTE: Hemorrhagic stroke is considered a neurological event and not as a separate bleeding event.

Cardiac Arrhythmias: Any documented arrhythmia that *results in clinical compromise* (e.g.,hemodynamic compromise, oliguria, pre-syncope or syncope) that requires hospitalization or requires a physician visit or occurs during a hospital stay. Cardiac arrhythmias are classified as one of two types:

- Sustained ventricular arrhythmia requiring defibrillation or cardioversion
- Sustained supraventricular arrhythmia requiring drug treatment or cardioversion

Pericardial Fluid Collection: Intervention or percutaneous catheter drainage. This event will be subdivided into those with clinical signs of tamponade (e.g. increased central venous pressure and decreased cardiac output) and those without signs of tamponade.

Hepatic Dysfunction: An increase in any two of the following hepatic laboratory values (total bilirubin, aspartate aminotransferase/AST and alanine aminotransferase/ALT) to a level greater than three times the upper limit of normal for the hospital, (or if hepatic dysfunction is the primary cause of death).

Major Infection: A new clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. The general categories of infection are listed below:

- Localized Infection: Infection localized to any organ system or region (e.g. mediastinitis) without evidence of systemic involvement (see sepsis definition), ascertained by standard clinical methods and either associated with evidence of bacterial, viral, fungal or protozoal infection, and/or requiring empirical treatment.
- *Endocarditis*: Signs, symptoms, and laboratory findings consistent with endocarditis, including but not limited to fever ≥ 38.0o C, positive blood cultures, new regurgitant murmurs or heart failure, evidence of embolic events (e.g., focal neurologic impairment, glomerulonephritis, renal and splenic infarcts, and septic pulmonary infarcts), and peripheral cutaneous or mucocutaneous lesions (e.g., petechiae, conjunctival or splinter hemorrhages, Janeway lesions, Osler's nodes, and Roth spots). Echocardiographic evidence of a new intra-cardiac vegetation with or without other signs and symptoms should be considered adequate evidence to support the diagnosis of endocarditis. TEE should be the modality of choice for diagnosis of prosthetic valve endocarditis.
- *Sepsis*: Evidence of systemic involvement by infection, manifested by positive blood cultures and/or hypotension.

Myocardial Infarction

Myocardial infarction (MI) should be classified when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis for myocardial infarction:

- *Myocardial Infarction*

  Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following:
  - Symptoms of ischemia;
  - ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]);
  - Development of pathological Q waves in the ECG;
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

- *Peri-CABG Myocardial Infarction*

  For CABG in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases in biomarkers > 5 x 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft of native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related MI.

- *Peri-Percutaneous Intervention (PCI) Myocardial Infarction*
  For PCI in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases in biomarkers > 3 x 99th percentile URL have been designated as defining PCI-related MI. A subtype related to a documented stent thrombosis is recognized. Sudden unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumed new ST elevation or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or autopsy, with death occurring before blood samples obtained, or at a time before the expected appearance of cardiac biomarkers in blood will be classified as a mortality due to MI.

Neurologic Dysfunction

Any new, temporary, or permanent, focal or global neurological deficit ascertained by a standard neurological examination (administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note). The examining physician will distinguish between a transient ischemic attack (TIA), which is fully reversible within 24 hours (and without evidence of infarction), and a stroke, which lasts longer than 24 hours (or less than 24 hours if there is evidence of infarction). The Modified Rankin Scale and the NIH Stroke Scale must be administered at time of event (within 72 hours following the event) and 90 days following the event to document the presence and severity of neurological deficits.
Each neurological event must be subcategorized as:

- Transient Ischemic Attack defined as an acute event that resolves completely within 24 hours with no imaging evidence of infarction.
- Ischemic or Hemorrhagic Stroke (Cerebrovascular Accident), defined as an event that persists beyond 24 hours or less than 24 hours associated with infarction on an imaging study. Hemorrhagic conversion of an ischemic stroke should be classified as ischemic.
- Toxic Metabolic Encephalopathy defined as a disorder of the brain function that arises from abnormal systemic metabolism or exogenous substances, altering awareness and/or consciousness, in which there is a non-focal neurological examination and a negative brain image.
- Other

Renal Events

Two categories of renal events will be identified:

- *Renal Dysfunction*
  Abnormal kidney function defined by > 100% rise in serum creatinine (Cr) from baseline, and Cr > 2.0
- *Renal Failure*
  New requirement for hemodialysis related to renal dysfunction. This definition excludes aquapheresis for volume removal alone.

Respiratory Failure
Impairment of respiratory function requiring re-intubation, tracheostomy or the inability to discontinue ventilatory support within 48 hours post-surgical intervention. This excludes intubation for re-operation or temporary intubation for diagnostic or therapeutic procedures.

Right Heart Failure
Symptoms and signs of persistent right ventricular dysfunction [central venous pressure (CVP) > 18 mmHg with a cardiac index <2.0 L/min/m2 in the absence of elevated left atrial/pulmonary capillary wedge pressure (> 18 mmHg), tamponade, ventricular arrhythmias or pneumothorax] requiring RVAD implantation, inhaled nitric oxide or inotropic therapy, for a duration of > 7 day.

Arterial Non-CNS Thromboembolism
An acute systemic arterial perfusion deficit in any non-cerebrovascular organ system due to thromboembolism confirmed by one or more of the following:

- Standard clinical and laboratory testing
- Operative findings
- Autopsy findings

This definition excludes neurological events.

Venous Thromboembolic Event
Evidence of venous thromboembolic event (e.g. deep vein thrombosis, pulmonary embolism) by standard clinical and laboratory testing.

Wound Dehiscence
Disruption of the apposed surfaces of a surgical incision, excluding infectious etiology, and requiring surgical repair.

Other An event that causes clinically relevant changes in the patient's health, or any event that is life-threatening, results in a fatality, results in permanent disability, requires hospitalization, or prolongs an existing hospital stay.

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Appendix 1:

New York Heart Association (NYHA) Classification

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New York Heart Association (NYHA) classification

NYHA grading		MET*
Class I	No limitations. Ordinary physical activity does not cause undue fatigue, dyspnoea or palpitations (asymptomatic LV dysfunction).	>7
Class II	Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnoea or angina pectoris (mild CHF).	5
Class III	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms (moderate CHF).	2–3
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of CHF present at rest (severe CHF).	1.6

***MET (metabolic equivalent) is defined as the resting VO_2**; for a 40-year-old 70kg man,[1] MET = 3.5mL O_2/min/kg body weight.

Reproduced from: National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (Chronic Heart Failure Guidelines Expert Writing Panel). Guidelines for the prevention, detection and management of chronic heart failure in Australia. Updated October 2011

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Appendix 2:

- **Six minute walk test (6MWT) recording form**

(Affix patient label here)

Patient ID:

Family name:

Given name(s):

Date of birth: **Sex:** ☐ M ☐ F ☐ I

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Six Minute Walk Test (6MWT) recording form

☐ Medical history checked

☐ Medical clearance provided for the patient to participate in exercise testing

Contraindications to 6MWT:

☐ Resting heart rate > 120 beats / min after 10 minutes rest (relative contraindication)

☐ Systolic blood pressure > 180 mm Hg +/- diastolic blood pressure > 100 mm Hg (relative contraindication)

☐ Resting SpO2 < 85% on room air or on prescribed level of supplemental oxygen

☐ Physical disability preventing safe performance

☐ No contraindications identified

6MWT 1						Date:	Time:
Supplemental Oxygen						Mobility Aid	
Time mins	BP	SpO2	HR	RPE	Distance walked	Rests / comments	
Rest							
1							
2							
3							
4							
5							
6							
Recovery 1							
3							

Total distance: _____ Symptom recovery: _____ HR recovery: _____

Limiting factor: _____

Was test terminated? ☐ No ☐ Yes If yes: when?

6MWT Termination Criteria:

☐ Chest pain or angina-like symptoms

☐ Heart rate > Predicted HR max.

☐ Evolving mental confusion, light-headedness or incoordination

☐ Physical or verbal severe fatigue

☐ Intolerable dyspnoea, unrelieved by rest

☐ Persistent SpO2 <85% (Note: pending clinical presentation)

☐ Abnormal gait pattern (leg cramps, staggering, ataxia)

☐ Other clinically warranted reason

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(Affix patient label here)

Patient ID:

Family name:

Given name(s):

Date of birth: **Sex:** ☐ M ☐ F ☐ I

HEART online
Heart Education Assessment Rehabilitation Toolkit

Six Minute Walk Test (6MWT) recording form

☐ Medical history checked

☐ Medical clearance provided for the patient to participate in exercise testing

Contraindications to 6MWT:

☐ Resting heart rate > 120 beats / min after 10 minutes rest (relative contraindication)

☐ Systolic blood pressure > 180 mm Hg +/- diastolic blood pressure > 100 mm Hg (relative contraindication)

☐ Resting SpO2 < 85% on room air or on prescribed level of supplemental oxygen

☐ Physical disability preventing safe performance

☐ No contraindications identified

6MWT 2						Date:	Time:
Supplemental Oxygen						Mobility Aid	
Time mins	BP	SpO2	HR	RPE	Distance walked	Rests / comments	
Rest							
1							
2							
3							
4							
5							
6							
Recovery 1							
2							

Total distance: _____ Symptom recovery: _____ HR recovery: _____

Limiting factor: _____

Was test terminated? ☐ No ☐ Yes If yes: when?

6MWT Termination Criteria:	
☐ Chest pain or angina-like symptoms	☐ Intolerable dyspnoea, unrelieved by rest
☐ Heart rate > Predicted HR max.	☐ Persistent SpO2 <85% (Note: pending clinical presentation)
☐ Evolving mental confusion, light-headedness or incoordination	☐ Abnormal gait pattern (leg cramps, staggering, ataxia)
☐ Physical or verbal severe fatigue	☐ Other clinically warranted reason

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Appendix 3:

– Minnesota Living with Heart Failure Questionnaire
– EQ-5D Health Questionnaire
– Duke Activity Status Index Questionnaire

MINNESOTA LIVING WITH HEART FAILURE® QUESTIONNAIRE

The following questions ask how much your heart failure (heart condition) affected your life during the past month (4 weeks). After each question, circle the 0, 1, 2, 3, 4 or 5 to show how much your life was affected. If a question does not apply to you, circle the 0 after that question.

Did your heart failure prevent you from living as you wanted during the past month (4 weeks) by -	**No**	**Very Little**				**Very Much**
1. causing swelling in your ankles or legs?	0	1	2	3	4	5
2. making you sit or lie down to rest during the day?	0	1	2	3	4	5
3. making your walking about or climbing stairs difficult?	0	1	2	3	4	5
4. making your working around the house or yard difficult?	0	1	2	3	4	5
5. making your going places away from home difficult?	0	1	2	3	4	5
6. making your sleeping well at night difficult?	0	1	2	3	4	5
7. making your relating to or doing things with your friends or family difficult?	0	1	2	3	4	5
8. making your working to earn a living difficult?	0	1	2	3	4	5
9. making your recreational pastimes, sports or hobbies difficult?	0	1	2	3	4	5
10. making your sexual activities difficult?	0	1	2	3	4	5
11. making you eat less of the foods you like?	0	1	2	3	4	5
12. making you short of breath?	0	1	2	3	4	5
13. making you tired, fatigued, or low on energy?	0	1	2	3	4	5
14. making you stay in a hospital?	0	1	2	3	4	5
15. costing you money for medical care?	0	1	2	3	4	5
16. giving you side effects from treatments?	0	1	2	3	4	5
17. making you feel you are a burden to your family or friends?	0	1	2	3	4	5
18. making you feel a loss of self-control in your life?	0	1	2	3	4	5
19. making you worry?	0	1	2	3	4	5
20. making it difficult for you to concentrate or remember things?	0	1	2	3	4	5
21. making you feel depressed?	0	1	2	3	4	5

11/10/04

EQ-5D Health Questionnaire

Client ID ☐ New User ☐ Existing User ☐

Date ☐

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ☐

I have some problems in walking about ☐

I am confined to bed ☐

Self-Care

I have no problems with self-care ☐

I have some problems with washing or dressing myself ☐

I am unable to wash or dress myself ☐

Usual Activities (*e.g. work, study, housework, family or leisure activities*)

I have no problems with performing my usual activities ☐

I have some problems with performing my usual activities ☐

I am unable to perform my usual activities ☐

Pain / Discomfort

I have no pain or discomfort ☐

I have moderate pain or discomfort ☐

I have extreme pain or discomfort ☐

Anxiety / Depression

I am not anxious or depressed ☐

I am moderately anxious or depressed ☐

I am extremely anxious or depressed ☐

Visual Analogue Scale

Please indicate on this scale how good or bad your own health state is today.

The best health state you can imagine is marked 100 and the worst health state you can imagine is marked 0.

Please draw a line from the box to the point on the scale that indicates how good or bad your health state is today.

Your own health state today

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐

PROVIDENCE
Heart and Vascular Institute

Duke Activity Status Index

The Duke Activity Status Index is a self-administered questionnaire that measures a patient's functional capacity. It can be used to get a rough estimate of a patient's peak oxygen uptake.

		Yes	No
1	Can you take care of yourself (eating, dressing, bathing or using the toilet)?	2.75	0
2	Can you walk indoors, such as around your house?	1.75	0
3	Can you walk a block or two on level ground?	2.75	0
4	Can you climb a flight of stairs or walk up a hill?	5.50	0
5	Can you run a short distance?	8.00	0
6	Can you do light work around the house, such as dusting or washing dishes?	2.70	0
7	Can you do moderate work around the house, such as vacuuming, sweeping floors or carrying in groceries?	3.50	0
8	Can you do heavy work around the house, such as scrubbing floors or lifting and moving heavy furniture?	8.00	0
9	Can you do yard work, such as raking leaves, weeding or pushing a power mower?	4.50	0
10	Can you have sexual relations?	5.25	0
11	Can you participate in moderate recreational activities, such as golf, bowling, dancing, doubles tennis or throwing a baseball or football?	6.00	0
12	Can you participate in strenuous sports, such as swimming, singles tennis, football, basketball or skiing?	7.50	0

Duke Activity Status Index (DASI) = sum of "Yes" replies _____

VO2peak = (0.43 x DASI) + 9.6

VO2peak = _____ ml/kg/min ÷ 3.5 ml/kg/min = _____ METS