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| **Project Title: Evaluation for cirrhotic cardiomyopathy: A prospective study of global cardiac function in decompensated cirrhosis and its clinical significance** |

**Project team roles and responsibilities of investigators and other key project team members.**

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**Resources**

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| What resources are necessary for the project to be conducted?  Blood tests, electrocardiogram and echo machines with special software programmes to calculate myocardial work index. |
| Please declare what funding support and amount is being sought or has been secured for this project**:**  **No**  Application submitted for Flinders Foundation Health Seed Grant 2020 but unsuccessful. |

**Background**

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| **Hypothesis** - *What is the scientifically valid research question being asked?*  We hypothesise that advanced and novel echocardiographic techniques such as global longitudinal strain (GLS) and myocardial work index (MWI) will be superior to conventional echocardiographic parameters in identifying cirrhotic cardiomyopathy (CCM) in decompensated cirrhosis. These measures have been shown to have improved diagnostic and prognostic value in several heart diseases. We plan to define a prognostic threshold of GLS/MWI towards development of critical clinical events in cirrhosis, such as hepatorenal syndrome, fluid overload, cardiac failure and death. We also plan to assess the reversibility of CCM by studying those with abnormal MWI and GLS after successful liver transplantation (LT) as there is uncertainty in this regard. |
| **Aims** - *What do the investigators intend to achieve with this research project?*  1. To evaluate for occult CCM in patients with decompensated cirrhosis using sensitive, advanced echocardiographic techniques such as GLS and MWI  2. To study the clinical correlation of these parameters with respect to the development of one or more of the following clinical events:   1. hepatorenal syndrome, 2. fluid overload, 3. cardiac failure, 4. death.   3. To assess the diagnostic and prognostic utility of serum markers of ventricular dysfunction and injury, such as N-terminal-pro-hormone BNP (NT-proBNP) and troponin in CCM and their correlation with echocardiographic indices  4. To assess reversibility of CCM with LT. |
| **Objectives**  1.By a prospective study of global cardiac function in patients with liver cirrhosis using GLS and MWI in addition to conventional transthoracic echocardiography and correlation of both findings.  2. If these indices are normal at rest, they will be studied under the effect of pharmacological stress with dobutamine.  3. Follow-up of the study cohort for 12 months with respect to complications such as hepatorenal syndrome, fluid overload, cardiac failure and death, with a view to establishing a critical threshold of GLS/MWI in CCM.  4. By correlating echocardiographic indices GLS/MWI with serum markers of ventricular dysfunction, such as NT-proBNP and prognostic markers of liver disease such as Model for End-Stage Liver Disease (MELD score).  5. By repeating the echocardiographic measures 12 months after LT in those with abnormal values prior to LT. |
| **Expected outcomes**  The study will provide the first ever description of GLS/MWI as diagnostic markers of CCM in decompensated cirrhosis and their clinical correlation. It will also compare conventional imaging with advanced modalities and establish their utility in CCM. It will stratify patients at high risk of complications for future adverse cardiovascular events, such as heart failure, hepatorenal syndrome and decompensation after bleeding, infection, transjugular intrahepatic portosystemic shunt or LT. It will provide valuable information regarding the reversibility of CCM with successful LT. |
| **Rationale / justification**  Despite a prevalence of up to 50%, CCM is relatively understudied as the diagnosis often becomes clear only under stressful conditions. Undetected CCM presents as fulminant cardiac failure at times of stress such as LT surgery, beta blockers, after the insertion of transjugular portosystemic shunt (TIPSS) and in response to sepsis. CCM in its severe stages becomes a contraindication to LT and is an important cause of morbidity and mortality following LT. The study aims to define an early diagnosis of cirrhotic cardiomyopathy using advanced, sensitive echocardiographic techniques. This will contribute to developing new diagnostic guidelines and improved case finding in patients with subclinical dysfunction.  We propose that measurement of these new indices in routine clinical practice will aid in identifying patients with cirrhosis at risk of developing hypotensive complications with non-selective beta blockers and optimise their management. Since these indices are measured also under pharmacologically induced stressful conditions, it will help uncover clinically occult cases of cirrhotic cardiomyopathy, particularly relevant in those considered for LT.  Given the absence of good quality data on the use of advanced echocardiographic techniques in this field, the study is expected to provide pivotal diagnostic and prognostic findings.  Research into treatment of cirrhotic cardiomyopathy particularly lacking. The study findings will guide towards future therapeutic trials in these patients. |
| **Literature review**  CCM is a systolic and/or diastolic dysfunction (DD) of the heart due to cirrhosis in the absence of a primary cardiac cause. It is an important cause of morbidity and mortality before and after LT. Despite its 50% prevalence,[1] it is relatively understudied as the diagnosis often becomes clear only under stressful conditions. Although there are instances of reversibility with successful LT, severe CCM may preclude LT.  Prognostic role of cardiac dysfunction in cirrhosis is increasingly evident. Worsening splanchnic vasodilatation and systemic vasoconstriction occur with progression of cirrhosis, resulting in low cardiac output and hepatorenal syndrome (HRS).[2] Cirrhotic patients with ascites frequently show evidence of DD at rest and with stress, compared to those without ascites.[3] DD detected in patients with advanced cirrhosis in a cohort of patients with normal serum creatinine was predictive of subsequent development of HRS, complications of portal hypertension and mortality.[4] Studies show a correlation of level of DD with severity of liver disease.[4, 5] In addition, structural changes (increase in left ventricular wall thickness) are reported in CCM.[6]  Non-selective beta blockers (NSBB), useful in primary and secondary prophylaxes for variceal haemorrhage, are shown to be unsafe in the setting of advanced cirrhosis with refractory ascites. It is recommended that NSBB use in advanced cirrhosis be guided by mean blood pressure and assessment of cardiac indices by invasive measurements.[7] Increased serum levels of brain natriuretic peptide (BNP) and pro-BNP, suggestive of ventricular stress, are reported in cirrhosis with cardiac dysfunction.[8] Accurate cardiac assessment is essential in patients undergoing transjugular intrahepatic portosystemic shunt (TIPSS) as it poses significant raise in preload and strain on right ventricle. The need for sensitive modalities in pre-LT assessment is advocated by increased frequency of cardiac adverse events, crucial causes of mortality after LT.[9]  Due to the combination of increased preload and decreased post-load, suitable imaging modality for its detection is unclear. Conventional 2D echocardiogram (2D Echo) findings of DD are preload dependent, and unreliable in situations of major fluid shift before and after paracentesis.[10] Myocardial strain measurements using tissue Doppler imaging (TDI) are more sensitive in identifying subclinical cardiac dysfunction even in setting of normal ejection fraction (EF).[11] Using TDI, DD was detected in 46% of cirrhotic patients in a prospective cohort study. Studies using speckle tracking echocardiography (STE) and TDI suggested that resting biventricular diastolic myocardial dysfunction be used as a new criterion for CCM.[12] Global longitudinal strain (GLS) measurement by STE is well validated to provide prognostically valuable information to complement EF assessed by routine 2D Echo.[13] There is limited information on TDI and STE in patients with advanced cirrhosis.[14]  Invasively measured left ventricular stroke work index (LVSWI) value <64.1 g-m/m2 in cirrhotic patients with refractory ascites on NSBBs was shown to be predictive of LT waiting list mortality.[7] There is growing evidence that MWI calculated by echocardiographic software, combines myocardial deformation (STE) with simultaneous blood pressure, is load independent, and well correlated with invasive LVSWI.  Studies employing MWI and GLS in the diagnosis of occult CCM and with potential clinical application are lacking and hence the current study is important. As pharmacological or exercise induced stress is supposed to uncover occult CCM, and in the absence of such studies evaluation of these parameters with dobutamine stress echo (DSE) as planned in the study is a uniquely original design. Furthermore, reassessment after a successful LT in those with abnormal echo parameters adds to the robustness of the study and makes it the first of its kind.  **References**  1. Bokarvadia, R., et al., Prevalence and clinical presentation of cirrhotic cardiomyopathy: A single centre experience from southern India. Indian J Gastroenterol, 2019. 38(2): p. 150-157.  2. Krag, A., et al., Low cardiac output predicts development of hepatorenal syndrome and survival in patients with cirrhosis and ascites. Gut, 2010. 59(01): p. 105-110.  3. Torregrosa, M., et al., Cardiac alterations in cirrhosis: reversibility after liver transplantation. J Hepatol, 2005. 42(1): p. 68-74.  4. Ruíz-del-Árbol, L., et al., Diastolic dysfunction is a predictor of poor outcomes in patients with cirrhosis, portal hypertension, and a normal creatinine. Hepatology, 2013. 58(5): p. 1732-41.  5. Yoshida, E.M., et al., Concordance of sustained virological response 4, 12, and 24 weeks post-treatment with sofosbuvir-containing regimens for hepatitis C virus. Hepatology, 2015. 61(1): p. 41-5.  6. Pozzi, M., et al., Evidence of functional and structural cardiac abnormalities in cirrhotic patients with and without ascites. Hepatology, 1997. 26(5): p. 1131-7.  7. Giannelli, V., et al., Impact of cardiac function, refractory ascites and beta blockers on the outcome of patients with cirrhosis listed for liver transplantation. J Hepatol, 2020. 72(3): p. 463-471.  8. Henriksen, J.H., et al., Increased circulating pro-brain natriuretic peptide (proBNP) and brain natriuretic peptide (BNP) in patients with cirrhosis: relation to cardiovascular dysfunction and severity of disease. Gut, 2003. 52(10): p. 1511-7.  9. Fouad, T.R., et al., Prediction of cardiac complications after liver transplantation. Transplantation, 2009. 87(5): p. 763-70.  10. Finucci, G., et al., Left ventricular diastolic function in liver cirrhosis. Scand J Gastroenterol, 1996. 31(3): p. 279-84.  11. Farr, M. and P.C. Schulze, Recent advances in the diagnosis and management of cirrhosis-associated cardiomyopathy in liver transplant candidates: advanced echo imaging, cardiac biomarkers, and advanced heart failure therapies. Clin Med Insights Cardiol, 2014. 8(Suppl 1): p. 67-74.  12. Rimbaş, R.C., et al., New Definition Criteria of Myocardial Dysfunction in Patients with Liver Cirrhosis: A Speckle Tracking and Tissue Doppler Imaging Study. Ultrasound Med Biol, 2018. 44(3): p. 562-574.  13. Potter, E. and T.H. Marwick, Assessment of Left Ventricular Function by Echocardiography: The Case for Routinely Adding Global Longitudinal Strain to Ejection Fraction. JACC Cardiovasc Imaging, 2018. 11(2 Pt 1): p. 260-274.  14. Sampaio, F., et al., Systolic and diastolic dysfunction in cirrhosis: a tissue-Doppler and speckle tracking echocardiography study. Liver Int, 2013. 33(8): p. 1158-65. |

**Project design**

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| **Research project setting -** The research will be conducted at the departments of Gastroenterology and Hepatology, and Cardiology, at Flinders Medical Centre and Lyell McEwin Hospital |
| **Methodological approach -** Rationale for choices of methods that are tied back to the aims/objectives:  Since the diagnosis of cirrhotic cardiomyopathy using advanced echocardiographic techniques is relatively underexplored, we have chosen a prospective observational cohort study design.  Results will be reported as frequencies or means + standard deviation (SD) plus  95% confidence interval (CI) of the mean. The Student t, Mann-Witney’s, and chi-squared tests will be used to compare continuous or categorical variables. Accuracy of global longitudinal strain (GLS) and myocardial work index (MWI) in predicting HRS and survival will be assessed by receiver operating characteristic. Echocardiographic parameters will be compared between baseline and post stress test and association with clinical outcomes will be measured. Univariate analyses will be to identify variables associated with development of type 1 HRS. Kaplan-Meier’s analysis will be used to estimate survival, and probability curves were compared by log-rank test. Multivariate analysis with cox regression will be used to identify variables associated with adverse clinical outcomes. |
| What are your outcome measures?  Thus, using the data collected, the project proposes to:  1. Define prevalence of CCM using GLS and MWI at rest and under pharmacological stress if required  2. Correlate GLS and MWI with LV systolic dysfunction measured by ejection fraction  3. Correlate GLS and MWI with diastolic dysfunction measured by E/e’ ratio  4. Study the association of CCM thus diagnosed with cirrhosis prognostic makers, such  as MELD score, aetiology of liver disease and specific complications of cirrhosis such refractory ascites and development of HRS, cardiac failure, and death  5. Provide a critical threshold of GLS/MWI as predictive of adverse clinical events  6. Analyse the correlation of cardiac biomarkers with echocardiographic indices  7. Assess the reversibility of CCM following successful LT. |
| **Project duration:**  Duration of enrolment period: 2 years  Follow-up: 1 year  Total duration: 3 years |

**Participant selection and activities**

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| **How many participants will be selected for the study?**  Sample size calculation  With a sample size of 78 subjects, the study will have 80% power to detect a 30% reduction in the composite outcome for a 1 SD increase in the MWI using Cox regression, assuming an R-squared of 30% with other variables and a two-sided type 1 error rate of alpha = 0.05.  Hence, we plan to recruit 80 patients over two years. |
| **How will participants be recruited into the study?**  Patients will be recruited either from liver outpatient clinics or during inpatient admissions.  From the database of the Chronic Liver Failure Programme, run by the chronic liver disease (CLD) nurses in the Hepatology unit, Flinders Medical Centre, a list of potential participants (patients with decompensated cirrhosis and ascites) will be prepared by the CLD nurses, who are a part of the regular medical care team.  These potential participants will be provided with an invitation letter providing preliminary information about the study. Study participation will also be discussed by the medical care team with identified patients during their next regular outpatient appointment or by phone call with CLD nurses. In addition, potential participants will also be approached while being admitted under the inpatient hepatology unit for management of cirrhosis and or LT assessment and given the invitation letter. If patients express interest in participation, subsequently a participant information and consent form (PICF) will be provided in person or by mail.  Similarly, at the Lyell McEwin Hospital, potential study participants who meet the study eligibility criteria will be provided with an invitation letter providing preliminary information about the study before approached by the medical care team either as in person or by mail. outpatients (during their routine visits) or as inpatients when they are admitted with hepatic decompensation. If patients express interest in participation, subsequently a participant information and consent form (PICF) will be provided |
| **What are the inclusion and exclusion criteria?**  **Inclusion: Inclusion criteria**  Male or female patients ≥18 years of age with diagnosis of liver cirrhosis (based on clinical, laboratory, endoscopic, and ultrasonographic features or on histology) will be included if they can provide informed consent and satisfy the following criteria  1. Consecutive cirrhotic patients with ascites and or past history of ascites on diuretics including  a) those requiring abdominal paracentesis,  b) hydrothorax requiring thoracentesis,  c) planned for TIPS.  2. Consecutive cirrhotic patients undergoing LT assessment with or without ascites.  **Exclusion: Cirrhotic patients with**  1. **ongoing** sepsis on inotropes;  2. ongoing grade 2–4 hepatic encephalopathy;  3. known coronary artery disease;  4. other known cardiac diagnoses such as valvular heart disease, dilated, hypertrophic and restrictive cardiomyopathy  5. Uncontrolled systemic hypertension  5. Contraindications to dobutamine, including:   * + Previous sensitivity to dobutamine   + Previous documented Ventricular Tachycardia or Ventricular Fibrillation |
| **Participant commitment** -What will their participation involve? *I.e. study visits, procedures, tests, tissue samples, questionnaires, wearing of any devices,*  The study involves a baseline study visit that includes blood tests and cardiac evaluation that includes electro- and echocardiography.  Evaluation by hepatologists/ registrars/ CLD nurses : The initial evaluation and consent will be done during a clinic appointment or during an inpatients’ stay. After obtaining consent, clinical profile including aetiology of liver disease, list of medications including the dose of beta blockers, and complications of portal hypertension will be recorded. Blood pressure and heart rate will be recorded. Blood tests for liver function tests, prothrombin time, serum creatinine, N-terminal-pro-hormone BNP (NT-proBNP) and cardiac troponin T levels will be done. The latter two are not standard tests performed in cirrhosis patients without any clinical manifestations of heart failure. Since the current study aims to uncover subclinical CCM, these tests are required.  Referral for echocardiography: Once the study consent is taken, study participants will be referred for echocardiography flagged with study details to be performed by technicians authorised by study personnel within the next 4 weeks . They will undergo a 12-lead electrocardiography (ECG) and a transthoracic echocardiography at the same visit**.** These are standard procedures in patients undergoing LT assessment, and in those with refractory ascites or hydrothorax prior to TIPSS insertion . In approximately 30% of study patients, this may not be the standard of care.  During the transthoracic echocardiography, standard echocardiographic data will be collectedincluding left ventricular ejection fraction (LVEF), ventricular dimensions and wall thickness, mitral inflow E, A, E/A ratio, mitral flow deceleration time and, if tricuspid regurgitation (TR) is present, then TR velocity and gradient study will be recorded. If regional wall motion abnormalities suggestive of ischemic heart disease are present or other cardiac abnormalities (valvular, ischemic, restrictive, obstructive cardiomyopathies, hypertensive heart disease) are incidentally detected, patients will be excluded from the study and appropriate referrals for further medical care will be made. Mitral annulus velocity (e’) will be calculated and E/e’ ratio (where E stands for trans mitral early peak velocity) and left atrial volume index (LAVI) will also be calculated. Using speckle tracking technique, from apical 4C, 2C and long axis, GLS will be calculated from pre-specified frame rates (70 fps, frames per second), and simultaneously blood pressure will be recorded. Using the special automated software MWI will be calculated from strain echocardiography combined with concurrent brachial blood pressure.  If the above imaging parameters are within normal limits, study participants will undergo dobutamine stress echocardiography (DSE) to uncover stress-induced LV systolic/diastolic dysfunction on the same day or within the next 2 weeks.  DSE will be performed as follows:  12 lead ECG for continuous monitoring throughout test.  Intravenous cannula inserted for Dobutamine infusion.  Dobutamine (250mg/100ml concentration) is infused for 3 minutes at 10mcg/kg/min, 30mcg/kg/min for 3 minutes and 50mcg/kg/min for 3 minutes. The target heart rate is 85% of predicted maximum heart rate (220 – age). If this is not achieved with Dobutamine alone a bolus of 300 to 600mcg of atropine may be given intravenously if not contraindicated.  Echocardiographic images from the parasternal and apical windows are obtained at rest and after each 3 minute dose, with final images at peak heart rate. For GLS and myocardial work an extra image of apical long axis would be required. BP is also monitored at 3-minutely intervals throughout test and into recovery.  Facilities for dealing with contingencies during DSE*:*  A cardiologist and usually an advanced cardiology trainee or fellow is present in the room during the study. Dobutamine is infused at low dose (5 to 10 mcg/kg/min) and incrementally increased. The half-life of dobutamine is only a few minutes and hence side effects dissipate quickly after cessation. In the rare event of a serious arrhythmia or cardiac arrest, the cardiologist would manage the situation with the help of the medical emergency team (MET) if needed. The SAHLN HREC will be notified if an adverse effect were to occur. |
| **Participant follow up** – *how are participants monitored during the study?*  Study participants follow-up will be done via electronic medical records or case notes.Those detected to have CCM by echocardiogram will be referred back to their respective clinicians for close monitoring and management according to the current treatment guidelines  Participants will be followed for 12 months from the time of inclusion in the study for the following events as a composite outcome: hepatorenal syndrome, refractory ascites, ascites/ renal- related unplanned hospital admissions, hypotension, cardiac failure and death. Any hospitalisation related to liver disease during the follow-up period will also be recorded**.** They will be censored at the time of LT.  Participants with pre-LT cardiac dysfunction will be followed up 12 months after LT to reassess its reversibility. If abnormal at study enrolment, N-terminal-pro-hormone BNP (NT-proBNP) and cardiac troponin T levels will be repeated. Blood forms will be sent out and tests can be coupled with regular blood tests. Follow-up echocardiogram will be organised around 12 months from LT. Echocardiographic parameters will be collected as per the description at baseline study.  Participants detected to have CCM by echocardiogram will be referred back to their respective clinicians for close monitoring and management according to the current treatment guidelines. |

**Consent**

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| **How you will be obtaining consent and/or what alternatives you will be using**:  At Flinders Medical Centre, potential study participants will be approached for study consent after preliminary information about the study is provided by phone call with CLD nurses, during regular clinic appointments, or hospital admissions. The consenting process will happen in clinics or in hospital wards in person.  At Lyell McEwin Hospital, potential study participants meeting the eligibility criteria will be approached and preliminary information will be given to them during their routine out-patient clinic visits or during in-patient admission. This will be followed up with a phone call to assess their interest in study participation. A follow-up appointment will be scheduled to complete the consent process for those interested in study participation. |
| **Which investigators will issue the information sheets and consent forms**:  All the investigators listed from the departments of Gastroenterology and Hepatology at Flinders Medical Centre and Lyell McEwin Hospital will be involved in the issue of information sheets and consent forms. |
| **How much time will participants have to consider participation**: Patients enrolled in the CLFP will have the information sheet mailed and will be given a few days before they are approached for consent (next clinic encounter). Inpatients will be given time from 24 hours till their date of discharge to consider study participation.  At Lyell McEwin Hospital, in-patients will be given time from 24 hours till their date of discharge to make a decision regarding participation. For out-patients, the follow-up phone call will be made a week after the preliminary information session.  Thus both inpatients and outpatients would have had atleast 24 hours to consider their study participation. |
| **Please specify which investigators will obtain consent from participants**: Except the clinicians directly involved in treatment decisions and the principal investigator(PI), all other nurses and doctors from the departments of Gastroenterology and Hepatology at Flinders Medical Centre and Lyell McEwin Hospital listed in this application will be involved in obtaining consent. In addition, members of the medical care team appropriately trained in obtaining informed consent will also be required to obtain consent. |
| **Will there be an opportunity to confirm or renegotiate consent during the research project**? –  Yes, study participants will be given an option to reconsider their study participation and withdraw at any time. |
| **Who will be confirming or renegotiating consent with participants and what process will be undertaken?**  The contact details of the PI at each site will be provided to the patients in the PICF and they will be informed to contact the person if they wanted to discuss the study participation further. The PI will have further discussions with study patients and apply their decision. |

**Data management –** as required in addition to that outlined in your HREA

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| **Who will collect the study data / information?**  The listed investigators and associate investigators will collect the study data. |
| **What format will the data or information be stored?**  In a password protected computer as an Microsoft Excel spreadsheet or in a statistical software document (IBM SPSS). |
| **Please provide details regarding training of the research team on maintaining the integrity and security of the data**  Researchers will utilise a two-level password protected computer to conduct the analysis. All data will be stored on this computer system, which can only be accessed by approved researchers. The de-identified data would be accessed only by the primary investigator and co-investigators mentioned in this application form. The de-identified data will be stored in the department’s desktop connected to the secure hospital server in the Department of Hepatology office (Flinders Medical Centre) and Department of Gastroenterology office at Lyell McEwin Hospital. These computers go into auto-locking mode after 5 minutes of inactivity and are password protected. After-hours, the entry to these offices would be restricted as they will be locked, and keys kept by the research team. The researchers involved in this study have prior experience in managing and protecting personal information as per the legislative requirements. |
| **What conditions can the data be accessed or granted to others?**  Only research investigators will have access to the data |
| **How will the research data be stored and what security measures are in place to protect it?**  Researchers will utilise a two-level password protected computer to conduct the analysis. All data will be stored on this computer system, which can only be accessed by approved researchers. The de-identified data would be accessed only by the primary investigator and co-investigators mentioned in this application form. The deidentified data that is collected will be stored in the department’s desktop connected to the secure hospital server in the Department of Hepatology office (Flinders Medical Centre). This goes into auto-locking mode after 5 minutes of inactivity and is password protected. After-hours, the entry to this office would be restricted as this will be locked and keys kept by the research team. The researchers involved in this study have prior experience in managing and protecting personal information as per the legislative requirements. |
| **How will you provide access to, disclose, use/re-use or transfer the data?**  Data will be transferred across hospitals by password protected emails sent via state health servers |
| **How long will the data be retained for?** Data should be retained to allow for sufficient time to allow reference to them by other researchers and interested parties.  The data will be stored for 15 years as per National Guidelines as detailed above. |
| **What plans are in place to store / archive the study data once the research is completed?**  Data will be archived as per SALHN protocols for archiving with Iron Mountain. Electronic documents will be stored as detailed above in a password protected computer. |
| **How will the study data be destroyed?**  All electronic data will be deleted/erased after 15 years, and all hardcopy data will be destroyed. |
| **Matching and sampling strategies:** not relevant |
| **Accounting for potential bias, confounding factors and missing information:**  By careful application of inclusion and exclusion criteria, potential bias and confounding factors will be avoided. Appropriate statistical input will be obtained to deal with missing data. |
| **Sample size and statistical or power issues**  With a sample size of 78 subjects, the study will have 80% power to detect a 30% reduction in the composite outcome for a 1 SD increase in the MWI using Cox regression, assuming an R-squared of 30% with other variables and a two-sided type 1 error rate of alpha = 0.05. |
| **How will you measure, manipulate and/or analyse the information collected?**  Since the diagnosis of cirrhotic cardiomyopathy using advanced echocardiographic techniques is relatively underexplored, we have chosen a prospective observational cohort study design.  Analysis will be done using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp. Results will be reported as frequencies or means ± standard deviation (SD) plus  95% confidence interval (CI) of the mean. The Student t, Mann-Whitney’s, and chi-squared tests will be used to compare continuous or categorical variables. Accuracy of myocardial work index in predicting HRS and survival will be assessed by assessed by receiver operating characteristic. Echocardiographic parameters will be compared between baseline and post stress test and association with clinical outcomes will be measured. Univariate analyses were will be to identify variables associated with development of type 1 HRS. Kaplan-Meier’s analysis will be used to estimate survival, and probability curves were compared by log-rank test. Multivariate analysis with cox regression will be used to identify variables associated with adverse clinical outcome. |
| **Data linkage –**what linkages are planned or anticipated?  Not anticipated |
| **What impact will a participant withdrawing have on the data and how will this be responded to?**  If a participant withdraws from the study, the data thus far collected will be reported. Appropriate statistical input will be obtained to deal with missing data. If the withdrawals are more than anticipated, application will be made to the ethics committee to increase the patient recruitment numbers and deadline. |

**Results, reporting, outcomes and future plans**

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| **Please detail your plans for the return of the research results to the participants**: Since the information obtained from the study is crucial to clinical management of the participants, it will be conveyed to the treating specialist physician and the general practitioner involved. If abnormal, an explanation and recommendations also will be provided.  If study results are normal, they will be sent by mail to the study participants. If abnormal, it will be discussed by the study team in person along with appropriate explanation and recommendations. |
| **What are your plans for dissemination and publication of project outcomes**:  We plan to present the study results as abstracts and papers in national and international conferences. In addition, every effort will be made to publish the reports in national or international peer reviewed journals |
| **Please detail other potential uses of the data at the end of the project**:  The data may be utilised to develop guidelines for the use of advanced echocardiographic techniques in the diagnosis and management of cirrhotic cardiomyopathy. |
| **What are your plans for sharing and/or future use of data and/or follow-up research?** i.e. anticipated secondary use of data:  Currently no follow-up research is planned. |
| **What is the project closure process?**  At the end of the study, all data will be stored/archived as per SALHN protocol. A final report form will be submitted to the Office for Research detailing results and any publications/presentations arising from the study. No further projects will be undertaken using this data. |