Partners Human Research Committee Detailed Protocol

Title: Pan-genotypic direct acting antiviral therapy in donor HCV-positive to recipient HCV-negative heart or simultaneous heart-kidney transplant

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I. Background and Significance

Donor heart availability continues to be a limiting factor in the number of cardiac transplants performed in the United States. While heart failure prevalence continues to rapidly rise the number of annual transplants has remained unchanged over the last decade.[1] This drives a growing disparity between cardiac organ supply and demand. In 2015 there were 4,183 patients awaiting cardiac transplant, while a total of 2,804 heart transplants took place.[2-3] As there continues to be a definite shortage of transplant viable organs in the U.S., it is of paramount importance and in accordance with the OPTN Final Rule that available resources are handled efficiently; namely, that all potentially transplantable organs are recognized for their enormous value as scarce resources and utilized to their maximum potential for the maximum benefit (the principle of Utility).[3]

In 2015 there were a total of 2,804 cardiac transplants performed in the United States[1]. In Region 1, which encompasses the New England states, there were 262 patients awaiting a heart transplant and a total of 97 cardiac transplants performed.[3] During the same one-year-period there were 41 HCV-positive donors who met standard criteria for cardiac donation, however these hearts were unfortunately discarded and not used for transplant given HCV-positivity.[4,5]

It has been well established that there exists a quality of life and survival benefit for patients with end stage heart disease who receive a well-functioning cardiac transplant.[6,7] Success with transplantation requires ongoing immunosuppression to prevent immune graft rejection, which can become complicated if persistent viral infection in donors is transmitted to recipients in the process of organ transplantation. However, given the severe shortage of available organs and significant waitlist mortality, the use of organs from HCV-positive donors has previously been considered.[8] Unfortunately there are limited studies investigating cardiac transplant outcomes in recipients with either pre-existing or de novo HCV infection, but conclusions drawn from the existing data state that the presence of HCV infection post-transplant, and the subsequent need for interferon based therapy, has been associated with poorer post-transplant outcomes and an increased risk of graft rejection.[9-20] These dated findings have led to guidelines recommending that otherwise acceptable heart donors be excluded on the basis of HCV infection.[21]

It is important to note that the above risks associated with transplantation of HCV-positive donor hearts were all determined prior to the current era of HCV treatment. Heretofore, the options for HCV treatment in the setting of cardiac transplantation have been severely constrained. Traditional anti-HCV therapy has depended on Interferon as the linchpin of single or combination therapy, and these Interferon based regimens have been generally poorly tolerated and correlated with an increased risk of serious systemic side-effects.[22] The potential association between the use of Interferon therapy and allograft rejection, necessitating a further increase in net immunosuppression to treat rejection, can cause an increase in viral replication, setting off a vicious cycle. This concern over graft rejection has been one of the most

formidable arguments against Interferon use in the immediate post-transplant setting. In addition to the Interferon-based HCV regimens being poorly tolerated and prone to complications, they have also produced underwhelming cure rates of approximately 50% (genotype 1).[23]

Direct acting antiviral agents (DAAs) have dramatically improved treatment options and outcomes for patients with HCV in both the pre-and post-transplant setting. Modern DAAs offer exceedingly high cure rates with minimal side-effects as compared to previous Interferon based treatment regimens.[23-25] SOLAR-1 was a large, multicenter, randomized controlled trial of sofosbuvir/ledipasvir with weight-based ribavirin in 223 liver-transplant recipients infected with HCV genotypes 1 and 4, with a wide range of liver disease severity. The cure rate for 12 weeks of combination therapy was 96%. In patients with HCV without cirrhosis in the allograft, cure rates of many DAA regimens have been reported in the range of 95% or higher. The discontinuation rate for these medications is low and side effects rare. Importantly, the sofosbuvir-based regimens do not have major interactions with the commonly used post-transplant immunosuppressive regimens.

The daily, fixed-dose, of co-formulated sofosbuvir (400 mg)/velapatasvir (100 mg) (Epclusa™) is similarly effective to its predecessor sofosbuvir/ledispasvir but has pan-genotypic activity. It is currently recommended as a first-line therapy for treatment-naïve, noncirrhotic HCV infection for genotypes 1-5. Reported cure rates in the non-transplant setting have been high in the 98-100% range. In the ASTRAL-1, ASTRAL-2 and ASTRAL-3 studies, more than 1,000 patients have been treated with Epclusa™ with an overall cure rate of 98%. Epclusa™ has not been approved in the U.S. for use in the post-transplant setting, but is approved in Europe based on existing safety and efficacy data. There is an ongoing study in New Zealand that has administered Epclusa™ for 4 weeks (starting immediately post-transplant). There have been no safety concerns and all recipients achieved rapid virologic suppression and remain negative through 4 weeks after completion of therapy. A second pan-genotypic DAA –glecaprevir (300mg)/pibrentasvir (120mg) (G/P, Mavyret™), has also recently been approved by the FDA. Reported cure rates are comparable to Epclusa™ (in the 99% range in ENDURANCE-1) and adverse reactions low with <1% of patients discontinuing therapy in the ENDURANCE-2 and ENDURANCE-3 trials. In light of these recent advances in HCV therapy, we believe that DAAs have the potential to play an important role in curtailing the current discard rates for HCV-positive donor organs. While the studies mentioned above are specific to liver transplantation, it is postulated that HCV cure, as confirmed by documentation of sustained virologic response (SVR), should be at least similar if not higher in transplantation of other non-HCV reservoir organs, such as heart. We hypothesize that utilizing DAA therapy can prevent or eliminate HCV infection post transplant when an HCV-positive heart is transplanted into a HCV naïve host.

If this approach proves successful, it has the potential to result not only in a large increase *in the number* of organs available in the cardiac donor pool but also an overall increase *in the quality* of organ offers. The reason for this is that, unfortunately, many potential donors who are HCV-positive belong to a young demographic, aged 18 to 35 years, who are now caught up in the national epidemic of opioid and intravenous drug abuse, their deaths resulting from drug overdosing. Sadly, despite availability of curative HCV therapies, very few intravenous drug users (IVDUs) are able to access these therapies. Thus, it is estimated that the HCV epidemic will continue to spread amongst young IVDUs throughout the foreseeable future. HCV-positive donor hearts originating from this potential donor cohort, by virtue of their young age and statistical estimates of projected allograft performance after transplantation, may be

some of the most robust in the cardiac donor pool. Demonstration of successful preemptive and/or immediate post-transplant treatment of HCV in this model could expand the viable cardiac donor pool and result in a reduction in morbidity, mortality, and long-term healthcare costs for patients with end stage heart disease.

Please note, throughout this protocol the use of HCV-positive refers to HCV nucleic acid testing (NAT)-positive organs. We address evaluation and management of NAT-negative organs under the Study Procedures section of this document and in the separate Protocol Summary document.

II. Specific Aims

***Primary Objective* - Aim 1**
Determine if preemptive administration of pan-genotypic direct-active antiviral (DAA) therapy in cardiac transplantation prevents the transmission of hepatitis C virus (HCV) infection from an HCV-positive donor heart to an HCV-negative recipient patient..

***Secondary Objectives* - Aim 2-3**
Aim 2
Evaluate the safety and tolerability of pan-genotypic DAA therapy in patients undergoing cardiac transplantation.

Aim 3
Determine the proportion of subjects with undetectable serum HCV RNA at study day 7, 14, 28, 56, 84, 112, 140, 224, and 365 in cardiac transplant recipients receiving pan-genotypic DAA therapy following transplant from an HCV infected donor

Clinical hypotheses
Hypothesis 1.
We hypothesize that preemptive administration of pan-genotypic DAA therapy following cardiac transplantation will be well-tolerated and halt the development of HCV infection in a transplant recipient as evidenced by a negative HCV viral RNA at 12 weeks post treatment.
Hypothesis 2.
We hypothesize that preemptive administration of pan-genotypic DAA therapy after HCV-positive donor heart transplantation will produce non-inferior survival results in recipient patients as compared to historical Scientific Registry of Transplant Recipients (SRTR) and The International Society for Heart and Lung Transplantation (ISHLT) data.

III. Subject Selection

- Cohort study (N=100)

This is a single center study evaluating if preemptive administration of pan-genotypic DAA therapy in cardiac transplantation prevents the transmission of hepatitis C virus infection from an HCV-positive donor heart to an HCV-negative recipient. Up to 100 patients will be enrolled study wide, with upto 50 total patients receiving transplant and treatment with study drug. We plan to enroll all 100 subjects and perform all 50 transplants at MGH.

Patients will be selected based on their diminished likelihood of receiving a heart from the waitlist within a period during which they would be likely to succumb to severe comorbidities. This will be determined in part through use of a patient's listing status (1A, 1B, 2) and clinical judgment.

To ensure maximal benefit for the recipient, only high quality donor hearts will be accepted as determined by 'traditional' cardiac donor selection criteria. These 'traditional' donor criteria, based on expert opinion and transplant experience, include: age less than 55 years, no history of chest trauma or cardiac disease, no prolonged hypotension or hypoxemia, appropriate hemodynamics (mean arterial pressure >60mmHg, central venous pressure 8-12mmHg), ionotropic support less than 10mg/kg/min (dopamine or dobutamine), normal electrocardiogram, normal echocardiogram, normal cardiac angiograph (if indicated by donor age and history), and negative serologies other than hepatitis C (including hepatitis B surface antigen, and human immunodeficiency virus).[21] Donors will be deemed acceptable if they meet 8 out of 8 traditional cardiac donor selection criteria.

1. Donor Inclusion/Exclusion Criteria
1a. Donor Inclusion Criteria:
Brain death diagnosed
Detectable HCV RNA
Traditional Donor Selection Criteria Met - acceptable for transplantation per usual evaluation

1b. Donor Exclusion Criteria:
Cardiac anatomical damage or significant pathology noted during recovery
Liver disease or signs of liver decompensation (splenomegaly, ascites, advanced fibrosis or cirrhosis)
Donor has been known to have previously received HCV treatment (interferon, ribavirin or DAA)
Any standard contra-indication to donation noted in donor (significant malignancy, infection with human immunodeficiency virus (HIV), prion-related disease, unusual infection).

2. Recipient Inclusion/Exclusion Criteria
2a. Recipient Inclusion Criteria:
Recipient is Age ≥ 18 years
Met MGH transplant center criteria, listed for cardiac transplant
Able to sign informed consent

2b. Recipient Exclusion Criteria:
Pregnant or nursing (lactating) women
HIV positivity
Any contra-indication to cardiac transplantation per center protocol
For study patients in whom Epclusa™ therapy is being considered, exclusion criteria includes patients on the following p-glycoprotein inducers or moderate to potent CYP inducers that cannot stop therapy: carbamazepine, phenytoin, phenobarbital, oxcarbazepine, rifabutin, rifampin, rifapentine, St. John's wort.
For study patients in whom Mavyret™ therapy is being considered, exclusion criteria includes patients on the following medications who cannot stop therapy: carbamazepine, rifampin, St. John's wort, and ethinyl estradiol-containing oral contraceptives.

For any patient receiving pan-genotypic DAA therapy, the corresponding drug administration instructions will be followed as listed in the Epclusa™ or Mavyret™ package insert. This includes review of potentially significant drug interactions and discontinuation or alteration in dosages and monitoring as

recommended. The Tables that will be followed can be found on the Epclusa™ package insert pg. 7 Table 2 and the Mavyret™ package insert pg. 8 Table 5.

A subset of patients awaiting cardiac transplant also require kidney transplant. The efficacy of DAAs in the treatment of donor derived HCV infection in kidney transplant has been documented in recent reports at the University of Pennsylvania and John's Hopkins Hospitals. Given this recent data, patients requiring simultaneous heart-kidney transplant (SHKT) are being considered for enrollment in this study. If patients screened for enrollment meet inclusion criteria for cardiac transplant, they will ***not*** be excluded based on the need for SHKT. Their case will be discussed with the study's transplant nephrologist, and enrolled accordingly with plans to update UNET listing status for SHKT HCV-positive transplant. As far as DAA therapy is concerned, if a patient is already undergoing treatment based on receipt of an HCV-positive heart, there are no changes in Epclusa™ or Mavyret™ therapy duration that would be required if a kidney transplant is also performed. In patients receiving SHKT, a patient's renal function and potential for delayed graft function (DGF) will come into play when determining initial DAA selection; we anticipate that Mavyret will be the therapy of choice in patients undergoing SHKT. As described above previously, we will adhere to the recommended dosing, medications adjustments, and monitoring as outlined in the Epclusa™ and Mavyret™ package inserts as documented in the detailed protocol.

Please note: Amiodarone use will not be a recipient exclusion criteria. This has been discussed with the cardiac surgeons and transplant cardiologists. For any patients on amiodarone prior to transplantation, pacing wires will be in place post-OHT (per usual protocol) with plans to monitor for bradycardia. In general patients no longer require amiodarone post-transplant, however to remain cautious during the wash-out period, the ability to pace symptomatically bradycardic patients will remain in place until amiodarone is out of the system or DAA treatment has been completed.

Standard of care at Partners includes confirming that female patients are not pregnant at the time of organ transplantation. For women of childbearing potential, a urine pregnancy test will be performed prior to enrollment. A negative result will be required at the time of transplant and prior to continuing study treatment.

IV. Subject Enrollment

This is a proof of concept, single center study for the donation of HCV-positive hearts to HCV-negative recipients, with preemptive treatment to prevent HCV transmission upon transplantation.

Any patient interested in learning about HCV infection and this study will be invited to voluntarily attend a one-on-one information session where they will be provided information on HCV including treatment options and its current role in cardiac transplantation. Patients will have the opportunity to ask questions throughout this meeting. After the session patients will be given the informed consent information to review at home. If interested they will subsequently return for a screening visit.

A study clinician investigator (licensed physician) will obtain informed consent. The consent form and protocol will be reviewed with the potential subject and any questions will be answered. The subject may be seen in a private area located in the Cardiology Clinic. Subjects will again have the option to take the consent form home with them for at least 24 hours to decide whether or not they wish to participate.

Ability to provide informed consent will be determined by the study investigator in discussion with the subjects treating physician. Subjects who cannot provide informed consent due to their clinical presentation will not be included. Surrogate consent will not be allowed in this study.

V. Study Procedures

Prior to enrollment in the study, research staff will be working with patient insurance to confirm that the patient insurer will be covering the cost of HCV treatment. In the event that insurance does not agree to cover the cost of HCV DAA therapy, the cost of medication will be covered by pre-established hospital funds.

Patients will initially sign informed consent to be "waitlisted" for HCV-positive donor hearts under this protocol. At the time a heart transplant becomes available, the "waitlisted" patients will be contacted and again sign informed consent for transplantation (standard of care).

Upon receiving notification that an HCV-antibody (Ab) positive donor organ is available, we will review if the organ is nucleic acid testing (NAT) positive or negative. A pre-emptive treatment approach will be used in patients receiving NAT-positive donor organs, and a reactive treatment approach will be performed in patients receiving NAT-negative donor organs, as outlined below:

A study patient who receives an HCV NAT-negative donor heart (or heart and kidney) will be followed with HCV viral load (VL) testing per study protocol (on study days 1, 3, 7, 14, 28, 56, 84, 112, 140, 224, 280, and 365)

- If the study patient does not develop a positive VL during this 365 day duration they will not undergo treatment with DAA therapy.
- If the study patient does demonstrate seroconversion *with a positive HCV VL* then we will initiate pan-genotypic therapy per study protocol. A patient's case will be reviewed and DAA selection made based on individual patient factors with plans to complete a DAA course and monitor for SVR at 12 weeks post-therapy completion.

Upon receiving notification that an HCV-positive donor organ is available with plans for transplantation, a patient's case will be reviewed and the appropriate DAA selected based on individual patient factors including current labs, medications, and anticipated future post-transplant therapies for any interactions that would preclude safe administration of DAA. **A study patient who receives an HCV NAT-positive donor heart (or heart and kidney)** will be scheduled to receive preemptive treatment with one of the following pan-genotypic DAAs:

- co-formulated sofosbuvir (400 mg)/velapatasvir (100 mg) (Epclusa^{TM}) given orally for a duration of 8 weeks post-transplantation.

OR

- co-formulated glecaprevir (300mg)/pibrentasvir (120mg) (Mavyret^{TM}) given orally for a duration of 8 weeks post-transplantation.

In summary: Patients who receive HCV NAT-negative organs are monitored with HCV VL testing as per usual protocol. HCV treatment is only initiated in patients who seroconvert *and* become NAT-positive.

Targeted physical assessment, vital sign measurements, emergence of adverse events and concomitant medication usage will be assessed at scheduled visits and as needed at the time of any unscheduled contact during the 56 day study period and/or the 365 day post-dosing safety follow-up.

Study visits post-cardiac transplantation will occur on days 0, 1, 3, 7, 14, 28, 42, 56, 70, 84, 112, 140, 224, 280, 365.

The **screening visit** will take place within an estimated 1-5 months prior to cardiac transplantation. When enrollment is complete the patient's insurer will be contacted to confirm coverage of a pan-genotypic DAA. **Day 0** of this study represents the day of cardiac transplantation, initiation of study drug will begin within 7 days of transplantation. After initiation of therapy, each subject will receive their study drug daily through course completion.

Pre-screening workup
Informed consent for evaluation
Completed education session with RN and MD/NP
Complete medical history
Complete physical exam
Laboratory screening (HCV Ab and VL, HIV, CMP, CBC with differential, Coagulation tests)
ECG monitoring
Quality of life assessment (SF-36)

Baseline testing (day of transplant, day 0)
HCV RNA, CMP, LFTs, CBC with differential, Coagulation tests
Review of concomitant meds

Week 1 (Visits on Day 3, 7)
HCV RNA, CMP, LFTs, CBC with differential
Adverse event reporting
Standard of care post-transplant visit
ECG monitoring
Review of concomitant meds

Week 2 (Day 14)
HCV RNA, CMP, LFTs, CBC with differential
Adverse event reporting
Standard of care post-transplant visit
Review of concomitant meds

Week 4 (Day 28)
HCV RNA, HCV Ab, CMP, LFTs, CBC with differential
Adverse event reporting
Standard of care post-transplant visit
Review of concomitant meds

Week 6 (Day 42)
HCV RNA, CMP, LFTs, CBC with differential
Adverse event reporting
Standard of care post-transplant visit
Review of concomitant meds

Week 8 (Day 56)
HCV RNA, CMP, LFTs, CBC with differential
Adverse event reporting
Standard of care post-transplant visit
Review of concomitant meds
Quality of life assessment (SF-36)

Week 9, (Day 63); One week post DAA completion
Tacrolimus level (for patients on Mavyret)

Week 10, SVR 2 (Day 70)
HCV RNA, HCV Ab, CMP, LFTs, CBC with differential
Tacrolimus level
Adverse event reporting
Standard of care post-transplant visit
Review of concomitant meds

Week 12, SVR 4 (Day 84)
HCV RNA, CMP, LFTs, CBC with differential
Adverse event reporting
Standard of care post-transplant visit
Review of concomitant meds

Week 16, SVR 8 (Day 112)
HCV RNA, CMP, LFTs, CBC with differential
Adverse event reporting
Standard of care post-transplant visit
Review of concomitant meds

Week 20, SVR 12 Visit (Day 140)
HCV RNA, CMP, LFTs, CBC with differential
Review of concomitant meds
Quality of life assessments (SF-36)

Week 32, SVR 24 Visit (Day 224)
HCV RNA, CMP, LFTs, CBC with differential
Review of concomitant meds

1 year visit (Day 365)
HCV RNA, CMP, LFTs, CBC with differential
Review of concomitant meds
Quality of Life assessment (SF-36)

Serum pregnancy tests (for all females of childbearing potential) will be conducted at screening and performed immediately prior to transplantation for all women of reproductive age as a standard of care. Because the effect, if any, of Epclusa™ or Mavyret™ on an embryo or fetus (developing baby still in the womb) is not known, patients may not participate in this study if they are pregnant, breastfeeding, or planning to become pregnant. Females who are able to become pregnant must agree to use adequate birth control use throughout the duration of the study. For the purposes of this study, adequate birth control means one of the following:

1. Intrauterine device (IUD)
2. Condom with spermicide
3. Diaphragm with spermicide
4. Complete abstinence (not having sex at all)

Hormonal forms of birth control including birth control pills, vaginal rings (like NuvaRung), implants (like Implanon), or injections (like Depo-Provera) may not work during treatment with Epclusa™ or

Mavyret™ and are not on the acceptable forms of birth control list. After patients have been off Epclusa™ or Mavyret™ for at least two weeks, they can again begin to use a hormonal form of birth control.

Men enrolled in the protocol must also agree to use adequate contraception while participating in this study. Adequate contraception is:

1. Condom with spermicide, and
2. Female partners must use an approved method of birth control as listed above

Men must also agree that they will not donate sperm during the entire study period.

Donor genotyping – HCV genotyping will be performed by the MGH Core Lab. Because the treatment in this study is pan-genotypic, we do not need genotype results to return prior to medication administration; delays in HCV genotyping will not influence initiation of the study drug.

Achievement of Sustained Virologic Response (SVR). Patients who received an **HCV NAT-positive** donor heart who have an undetectable viral load 12 weeks after completing therapy (SVR 12) are patients in whom the use of DAA has successfully prevented HCV infection transmission. If during monitoring for these patients a positive viral load is detected and at the end of their 8 week therapy course, a plan will be made to extend the patient's course of Epclusa™ or Mavyret™ from 8 weeks to 12 weeks. We may also add additional Hep C medications to increase the chance of curing the Hep C infection. If this happens, we will plan to review all of these details in person with the patient and determine, based on recent updates and clinical practice, the best regimen with which to treat the patient and achieve HCV cure.

This study has received IND exemption from the FDA regarding use of pan-genotypic DAA therapy; a letter has been posted on the Attachments tab in Insight to provide documentation.

VI. Biostatistical Analysis

Variables/Time Points of Interest

The primary variable of interest will be HCV RNA at the multiple time-points assessed during and after treatment.

The primary efficacy outcome "Prevention of HCV Transmission" will be determined by a negative HCV RNA test.

The safety outcomes include summation of treatment related adverse events and transplant rejection or patient mortality. On treatment eGFR, proteinuria, hemoglobin, and liver function tests will be summarized to assess safety.

Statistical Methods

Patient characteristics for this cohort (N=50 receiving HCV+ organ) will be presented with summary statistics for baseline demographics and clinical variables. The SVR12 rate will be presented and 95% CI constructed with the exact test. Mean and standard deviation for on-treatment laboratory values will be presented to analyze safety.

Power/Sample Size:

This is a pilot study. Up to 100 patients will be enrolled (consented for the possible receipt of an HCV-positive organ), the total number of patients eligible to receive transplant and study drug = 50.

VII. Risks and Discomforts

Psychological risk
Participation in research may result in undesired changes in thought process or emotion (episodes of depression, stress, guilt). Patients may experience discomfort when being asked questions about their medical history that they deem to be private.

Risks related to transplantation with an HCV infected heart (or heart and kidney)
Liver problems
While unlikely, it is possible that DAAs will not result in the same efficacy following cardiac transplant. If HCV is transmitted and not eradicated it is possible that HCV infection post-transplant could cause health problems, including liver injury. In the short term, infection with HCV can cause a flu-like illness that includes fatigue, nausea, fever, abdominal pain, vomiting, joint pain, and yellowing of the skin (jaundice). Although it is very rare, infection with HCV can cause severe inflammation of the liver or even liver failure, including a condition called fibrosing cholestatic hepatitis. The risk of this complication in patients without HCV who receive a transplant from a donor with HCV is unknown. This complication can be treated and cured in the majority of cases with the HCV medications.

Cirrhosis of the liver can cause someone to experience leg swelling, yellow skin, skin itching, abdominal bleeding, shortness of breath, and the abdomen to fill with fluid (ascites). Liver failure can also cause death. Based on the limited data available, it would be extremely rare for someone in the study to experience liver failure in the first few months after transplantation because the study will be giving HCV treatment right away.

In the unlikely event that the patient develops HCV infection despite DAA therapy, we will be prepared to offer 2nd line treatment using + ribavirin or Mavyret™ + ribavirin plus an additional DAA agent. In the unlikely event that this fails, there may be continued inflammation and scarring of the liver that over many years (10-30) that can lead to cirrhosis. If HCV causes cirrhosis, the patient is at increased risk of developing liver cancer, liver failure requiring a subsequent liver transplant, or death. Of note, we anticipate that with study drug treatment, or if necessary additional HCV therapies, we will be able to successfully prevent transmission and eradicate HCV in our study population.

Additional risks of HCV:
HCV can cause other types of inflammation in the body, such as arthritis, rash, anemia, nerve pain and inflammation damage to your kidney transplant. These problems are rare, and affect less than 2% of people who have HCV. These problems should respond to effective HCV treatment.

Risks Related to Study Medications

Risks of sofosbuvir/velapatasvir (Epclusa™)
Sofosbuvir/velapatasvir (Epclusa™) is an FDA approved pan-genotypic regimen for treating HCV infection. Thousands of patients have received this medication for HCV treatment.

In patients receiving Epclusa™ for 8 weeks the most common side effects were fatigue, headache, and nausea (occurring in approximately 1 in 10 patients). Only 0.2% of patients had side effects so severe that they had to stop treatment.

The safety and tolerability of Epclusa™ after cardiac transplantation has not yet been extensively studied. It is possible that taking immunosuppressant medications needed after cardiac transplant may change the effectiveness or side effects of Epclusa™.

Risks of glecaprevir/pibrentasvir (Mavyret™)
Glecaprevir/pibrentasvir (Mavyret™) is an FDA approved pan-genotypic regimen for treating HCV infection. Thousands of patients have received this medication for HCV treatment.

The adverse reactions data for Mavyret™ in subjects without cirrhosis were derived from nine Phase 2 and 3 trials which evaluated approximately 2,300 subjects infected with HCV genotype 1, 2, 3, 4, 5, or 6 who received Mavyret™ for 8, 12 or 16 weeks. In patients receiving Mavyret™ the most common side effects were headache (13%), fatigue (11%), and nausea (8%). The overall proportion of subjects who permanently discontinued treatment due to adverse reactions was 0.1% for subjects who received Mavyret™ for 8, 12 or 16 weeks.

The safety and tolerability of Mavyret™ after cardiac transplantation has not yet been extensively studied. It is possible that taking immunosuppressant medications needed after cardiac transplant may change the effectiveness or side effects of Mavyret™.

Risk of allergic reaction
As with any drug, an allergic reaction can occur. Allergic reactions can be mild or serious, and can even result in death in some cases. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing.

Risks Related to Study Procedures

Risks of Blood Draws
The patient may have a bruise (a black-and-blue mark) or pain where researchers take the blood samples. There is also a small risk of feeling lightheaded, fainting, or infection. A total of up to 53 tablespoons of blood will be drawn over the course of the entire study.

Risks to an Embryo or Fetus, or to a Breastfeeding Infant
Because the effect, if any, of Epclusa™ or Mavyret™ on an embryo or fetus is not known, the patient may not participate in this study if they are pregnant, breastfeeding, or planning to become pregnant. This is not a new requirement necessitated by this protocol, as patients on the cardiac transplant list must also agree to not become pregnant while awaiting and for a period of time after transplantation.

Study Drug Exposure
Patients will not receive the study drug until post-transplant or just prior to their transport to the operating room (OR) to receive a donor organ. We anticipate that the likelihood of a patient not receiving an organ after taking a dose of study drug is extremely low. However, in the event that a patient does receive the initial dose of study drug and not an HCV-positive heart, we would then plan to immediately stop the study drug. No additional study drug would be given unless the patient was again offered an HCV-positive organ and returning to the OR.

VIII. Potential Benefits

Receipt of an organ

Participants may receive a cardiac transplant because they are enrolled in this study. For some patients, they may have not received an organ at all if the severity of their disease would have otherwise led to death while awaiting organ transplant.

Shortened wait time
Participants may spend a shorter duration of time on the transplant waitlist than they otherwise would have if they had not been a part of the research study.

Improved patient quality of life
A heart that would have otherwise gone to waste can potentially be used to prolong the life and significantly improve morbidity for an individual.

Cost Reduction
This procedure could also eliminate costs associated with the management of end stage heart disease and hospitalization.

Increase organ donor pool (an otherwise stagnant number)
This study could increase the number of viable hearts for transplant and greatly reduce the HCV-positive cardiac discard rate.

IX. Monitoring and Quality Assurance

An independent data safety monitoring board (DSMB) will not be used in this study as it is an open label study, will have low enrollment, and will only take place at 1 site.

Once a patient is enrolled, Dr. Lewis, Dr. Chung, Dr. Bethea, and Dr. D'Alessandro will meet in person every three months to review any safety concerns. More frequent meetings will occur if needed.

Dr. Lewis and Dr. Chung will be regularly monitoring the study documents for accuracy and meeting with study staff to review the study status. This protocol will be incorporated into the cardiology standard of care post-transplant protocol. A pool of heart failure attendings, including Dr. Gregory Lewis, Dr. Stephanie Moore, Dr. Erin Coglianese, Dr. Sunu Thomas, and Dr. William Carlson will potentially be caring for the patients enrolled in this study. Dr. Lewis will ultimately be responsible for protecting the rights, safety and welfare of all subjects enrolled in this study. In the case of Dr. Lewis's absence, monitoring responsibilities will be delegated to one of the subinvestigators listed on the 1572 as well as the IRB protocol application.

Adverse events will be thoroughly assessed at each treatment visit. Adverse events will be reported to the HRC as per current guidelines. We plan to comply with the reporting of any IND safety reports or any other federal regulations. The study coordinator will work with the physician investigators to process the report of these events as they happen.

Adverse events and unanticipated problems involving risks to subjects or others will be reported to the PHRC in accordance with PHRC adverse event and unanticipated problems reporting guidelines.

Dr. Lewis will ensure that all adverse events are reported according to the PHRC guidelines.

Dr. Lewis and the study staff will meet monthly to review the accuracy and completeness of case report form entries, source documents, informed consent, and all regulatory documents.

X. References

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4. OPTN Final Rule §121.8 Allocation of organs, 64 FR 56659, Oct. 20, 1999, as amended at 64 FR 71626, Dec. 21, 1999.
5. Data from New England Organ Bank (NEOB): http://neob.org/
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