Study Protocol, Statistical Analysis Plan, and Informed Consent for Utilization of Hepatitis C Positive Kidneys in Negative Recipients (USE-Hep C)

I. Objectives

To evaluate the safety and feasibility of transplanting kidneys from Hepatitis C virus (HCV) infected donors into recipients without HCV infection

II. Background and Rationale

a. Background

Patients with end stage renal disease (ESRD) have increased mortality compared to their healthy peers with a five years survival chance of 42-52% in hemodialysis and peritoneal dialysis patients respectively. Over the last decade, the number of ESRD patients has risen significantly. In 2015, there was over 124,000 new cases and 703,243 prevalent cases of ESRD in the United States (1a). Kidney transplantation remains the preferred treatment modality. Successful kidney transplantation is associated with improved survival, improved quality of life and health care cost savings when compared to dialysis. However, the gap between patients in needs and available organs remains large. In 2017, there were over 94,000 patients waiting on the deceased donor kidney transplant waiting list with only 28,588 deceased donor transplantation performed(1). This organ shortage along with the advances in the available treatments of transmittable diseases such as human immunodeficiency virus (HIV) and hepatitis C virus (HCV) has prompted the transplant society to explore donors previously believed to be an acceptable candidate for donation.

Traditionally, HCV donor positive (HCV D+) kidneys were offered only to HCV positive recipients due to a 100% HCV transmission risk. Due to the low numbers of kidney transplant candidates who are also HCV positive, many of these kidneys are discarded. The development of direct acting anti-viral drugs (DAAs) have transformed the realm of HCV therapy. DAAs has turned HCV hepatitis into a highly curable condition with cure rates exceeding 95% for all different HCV genotypes 1 through 6(2-6).

DAAs can be safely used in all solid organ transplantation. Sofosbuvir/velpastasvir (Epclusa) combination was used for treatment of recurrent HCV infection (genotype 1 through 6) after liver transplantation (3, 5, 7). A 12 weeks treatment resulted in overall 96% cure rate in patients with and without cirrhosis. The drug combination was very well tolerated and had minimal interaction with immunosuppressants. Once daily Glecaprevir/pibrentasvir (Mavyret) combination was used to treat HCV infection (genotype 1 through 6) in 80 liver transplant and 20 kidney transplant recipients in the MAGELLAN-2 study(8). The overall cure rate was 98% at 12 weeks post-treatment. The drug combination was again very well tolerated.

These advances in the treatment of HCV infection has made it possible to entrain the use of organs from HCV viremic patients into non infected HCV recipients with plan for HCV treatment post transplantation

b. Rationale:

DAAs are highly tolerated by patients and carry a cure rate of >95%. This favorable side effect profile and high efficacy can help expand the pool of available organs by increasing the utilization of organs from HCV infected donors. Over the past decade, the opioid crisis have increased the number of HCV infected deceased donors. These donors are usually young with fewer comorbid conditions such as diabetes and hypertension. Organ procured from such donors are usually of good quality. The transmission rate of HCV when using infected organ is guaranteed but the availability of DAAs make this less of a concern. This scenario has been tested and proven safe by other groups. The EXPANDER (Exploring Renal Transplant Using Hepatitis C Infected Donors for HCV- Negative Recipients) group at Johns Hopkins University performed transplantation of kidneys from HCV+ into 10 HCV- recipients(9). The group used **elbasvir-grzoprevir** (supplemented with sofosbuvir for genotype 2, 3) started before transplant and continued for 12 weeks post-transplant. There were no treatment related adverse effects. HCV virus was undetectable with stable liver function in all recipients 12 weeks after completion of treatment.
Another group, the THINKER (Transplanting Hepatitis C kidneys Into Negative Kidney Recipient), from the University of Pennsylvania also used similar drug combination elbasvir-grazoprevir (Zepatier) in 20 HCV negative recipients who received kidneys from donor infected with HCV genotype -1(10). The group reported a 100% transmission rate of HCV with 100% cure rate as evident by undetectable HCV pcr in the blood 12 weeks post treatment. There were again no treatment related adverse events. Kidney allograft function was excellent at 6 and 12 months.

The use of HCV + donors into negative recipients has also been investigated in thoracic organ transplantation including heart (11) and lung (12, 13). Patients in these reports were treated by either Sofosbuvir/Ledipasvir (Harvoni) if they contacted HCV genotype 1 or Sofosbuvir/Velpatasvir if they contracted other genotypes. All of the reported cases had complete cure of HCV transmitted after transplant and no treatment associated adverse effects.

Giving the large body of evidence supporting the safety and efficacy of DAAs in treatment of HCV in the transplant recipients, we at the Ohio State University, would also like to explore the safety of transplanting HCV positive kidneys into negative recipients in our program. We hope to incorporate this a standard practice for patients who consent to receive HCV + donor kidney.

We plan on using Sofosbuvir/Velpatasvir (Epclusa) as our first therapy choice. Our choice for Epclusa stems from the fact it's a daily one tablet preparation (improving patient's treatment adherence), has minimal drug-drug interaction with immunosuppressive drugs,

and is equally effective again all different HCV genotypes without needs for supplemental therapy. Epclusa has been studied in liver transplant patients and proven to be effective and very well tolerated (7). The one important caveat with Epclusa is its need for dose adjustment in renal failure. Hence, we plan on using Glecaprevir/Pibrentasvir (Mavyret) as agent of choice in patients who develop delayed graft function or continue to have poor allograft function with estimated glomerular filtration rate (eGFR) <30 ml/min by one to two weeks post-transplant. Mavyret does not require dose adjustment based on renal function and is equally effective against all different HCV genotypes. It was also studied in liver and kidney transplant patients and proven highly effective and well tolerated (8). Sofosbuvir/Velpatasvir or elbasvir/grazoprevir will be used as a third-line drug based on the HCV genotype in case of coverage denial of the first and second-line drugs by the patient's health insurance.

c. Significance:

DAAs has the potential to turn HCV infection into a condition similar to cytomegalovirus (CMV) infection. Currently, it's a routine and completely acceptable practice to transplant organs from CMV+ donors to CMV- recipients. These recipients are at very high risk for CMV infection. In the absence of preventive measures, 40 to 100% off all kidney transplant patients will develop CMV infection and up to 67% will develop CMV disease that could be life threatening(14, 15). Such risk is greatly ameliorated by the presence of active treatment for CMV infection in the form of ganciclovir, cidofovir and foscarnet. Similarly, DAAs are effective and very well tolerated treatment that should make transplanting HCV positive organs into negative donors possible.

It is hard to accurately estimate the number of additional donors that could be available if HCV+ organs are being used routinely. It's estimated that between 2005 and 2014 about 4,144 kidneys from HCV+ donors were discarded(16). Many more kidneys from HCV infected donors were probably never procured because of fear of lack of appropriate recipients. Over 8000 lives could have been saved have these kidneys been utilized. Additionally, accepting kidneys from HCV+ donors can shorten patients waiting time on the deceased waiting list(17). This in turn results in improved survival and overall quality of life and decreased health care costs. A cost effectiveness analysis compared the cost associated with accepting HCV+ donor kidney followed by DAAs vs remaining on dialysis while awaiting for HCV- kidney found a total cost saving of about $138,000 per patient(18).

We believe HCV positive donor organs are being underutilized in the current era of DAAs. We hope to provide further proof to the safety and utility of the strategy of transplanting HCV positive donor into negative recipient. We hope such proof will encourage transplant leaders, organ procurement organizations, and payers to invest into building an infrastructure that can turn such strategy into standard of care and ensure access and coverage for a variable selection of HCV therapies.

III. Procedures

a. Research design:

This will be an open label, prospective, interventional, proof of concept study to evaluate the feasibility and safety of kidney transplant from HCV positive donors into HCV negative donor using Sofosbuvir/Velpatasvir as the preferred treatment choice for post-transplant HCV transmission.

The Ohio (OSUMC) has performed HCV+ into HCV- recipient liver transplants as standard of care since February of 2019. OSUMC has also been performing transplant of liver and kidneys from donors who are HCV antibody positive but PCR negative (non-viremic donors) since 2016. In order to present an overall picture of the patient outcomes across multiple types of organ transplants using HCV+ organs, we would like to review data from these liver and kidney transplant patients. To do so, retrospective data from recipients of HCV positive into negative liver transplants, and HCV antibody positive but PCR negative liver and kidney transplant recipients will be analyzed. Patients who were treated between January 19th, 2016 and November 26th, 2019 will be included in our analysis.
In order to confirm the safety of transplants using HCV+ kidneys, we will compare the outcomes of transplant from HCV viremic donors (HCV PCR+) to those from HCV non viremic doors (donors with HCV antibody neg/PCR negative and HCV antibody positive/PCR negative). To do so, we will retrospectively review charts of patients who received a kidney transplant at OSU between 1/1/2018 and 8/1/2020. This review will include recipients of HCV antibody negative/PCR negative (antibody (ab)-/Nucleic Antigen Test (NAT)-), HCV antibody positive/PCR negative (ab+/Nat-), and HCV antibody positive/PCR positive (ab+/Nat+).

b. Study sample:

The study will aim to enroll 55 patients. Giving the fact this is a proof of concept study, a sample size cannot be calculated based on power analysis.
Patients will be screened by a research nurse after completion of their pre-transplant evaluation. Patient who meets all inclusion and none of the exclusion criteria will be approached for consent. The consent will be discussed and explained to patient by a physician or research coordinator.

Inclusion criteria:
Adult age >18 years able to provide consent
Lack of available living donor
Calculated pre-transplant reactive panel (cPRA) of <80%
Estimated post-transplant survival (EPTS) index >20% and <80%
Negative pre-transplant HIV, HCV, and HBV serology and blood PCR
No clinically significant pre-transplant liver disease
Contraception based on the REMS protocol
Agree to abstinence form alcohol for at least 6 months post-transplant
Exclusion criteria:
Living donor available
Dialysis time >5 years

History of previous organ transplantation
Listing for multi-organ transplantation
Active or recent history (<6 months) of alcohol or substance abuse
Clinically significant liver disease as determined by principal investigator
History of hepatocarcinoma
Pregnancy or lactation
Refusal to accept blood transfusion
HIV infection
HCV pcr or antibody positive
HBV infection
Any condition that in the opinion of the investigator would impair the patients' ability to comply with the study procedures
Donor selection criteria;
Positive HCV PCR at time of donation
KDPI<85%

For the retrospective chart review of HCV+ liver/HCV- recipients and HCV antibody positive/PCR negative liver and kidney transplant recipients, we aim to review 78 charts. The Ohio State University has so far performed 11 HCV+ into negative liver transplant, 25 HCV ab+/PCR negative kidney transplant and 25 HCV ab+/PCR negative liver transplant so far., Since this is a retrospective chart review portion of the study, a waiver of consent and HIPAA authorization will be requested for this portion of the study.

c. Measurements/End points:

Primary efficacy end point is the proportion of patients with undetectable HCV PCR at 12 weeks after completion of HCV treatment with Sofosbuvir/Velpatasvir
Primary safety end point: The incidence of adverse events related to DAA treatment
Secondary end points:
eGFR and serum creatinine at 6 and 12 months post-transplant
Patient's survival at 6 and 12 months
Graft's survival at 12 months

d. Detailed study procedures:

After completion of post-transplant evaluation and signing informed concept, patient status at UNOS will be changed to "Willing to accept HCV+ organ". Once an organ become available, it will be offered to the patients on HCV+ list per UNOS points system. Care following receiving HCV+ donor kidney for study patients will be as follow

1. Induction/maintenance therapy:
    I. Patient will receive induction with Thymoglobulin (rabbit ATG) for a total dose of 4-6 mg/kg per routine center protocol. Thymoglobulin induction will be started on day 0 after transplant surgery.
    II. Maintenance immunosuppressive therapy: patient enrolled in the study will receive the same routine maintenance immunosuppressive therapy used for recipients of HCV negative kidneys in our center. Maintenance

therapy will be started on post-operative day 1 with Tacrolimus, Mycophenolic acid, and rapid prednisone taper. Tacrolimus will be started at a weight based total dose of 0.15 mg/kg divided into two daily doses 12 hours apart. Trough levels will be checked daily prior to morning dose while inpatient and dose will be adjusted to target trough level of 8-12 for the first three months. Trough levels target in enrolled patients will follow our center post-transplant Tacrolimus trough target. Mycophenolic acid will be started at dose of 720 mg twice daily on post-Operative day one and continued long term. Dose can be adjusted/reduced per patient's primary transplant physician as appropriate due to side effect or infectious complications. Prednisone therapy will be tapered off by day 4 per center protocol

2. Hepatitis C evaluation and treatment:
   I. Recipients will have HCV PCR checked on admission day 0 prior to kidney transplant, and on day 3 prior to discharge. Patient with negative HCV PCR prior to discharge will have PCR checked weekly for 8 weeks then monthly up to 12 months post-transplant until PCR is positive. Checks will be stopped once PCR is positive. Patients with positive HCV PCR at day 3 post-transplant will not have further weekly or monthly checks but will follow the during treatment/post-treatment HCV PCR schedule mentioned below in section 2.3.d.

   II. Hepatology consult will be placed automatically on day 0 of transplant index admission and again if the patient is symptomatic for HCV.

   III. Direct acting anti-viral drugs (DAAs) will be initiated within eight weeks of first positive HCV PCR.
      a. Sofosbuvir/Velpatasvir will be first line therapy. Treatment will be with one tablet a day for 12 weeks.
      b. Glecaprevir/Pibrentasvir will be a second line therapy for patients with delayed graft function or poor graft function (eGFR <30) two weeks post-transplant. Glecaprevir/Pibrentasvir doesn't require renal dose adjustment. Treatment will be with 3 tablets daily for 12 weeks.
      c. Other FDA approved DAAs could be utilized as potential third line therapies if the first and second line therapies are not approved by insurance or patient could have a potential drug to drug interactions
      d. Patient will receive follow up HCV PCR on week 4 and week 12 of therapy. HCV PCR will be repeated on week 12 following completion of DAA therapy.

3. Clinic schedule follow up:
   I. Patient will be seen in the transplant clinic per routine post-transplant protocol; weekly x4, then on weeks 6, 9 and 12, then months 4,6,9 and 12, 18 and 24.

II. Patient will be seen by Hepatology only if the patient is symptomatic for HCV.

4. Laboratory schedule:
   I. Patient will have CBC, Chem-7, and Tacrolimus trough levels drawn twice weekly for the first 12 weeks, then once a week 3-6 months, then every two weeks 6-12 months, then once a month thereafter (standard of care)
   II. Liver function test (LFTs), Prothrombin time (PT), and Partial Thromplastin Time (PTT) will be checked weekly for the first 12 weeks then quarterly per center protocol
   III. HCV PCR will be checked on week 4 and week 12 of therapy. HCV PCR will be repeated on week 12 following completion of DAA therapy then quarterly for one year Lipid profile, HbA1c, iron studies and alloscreen will be checked per center protocol

e. Data and statistical analysis:

I. Data presented will be mostly a descriptive data giving low number of enrolled patient and lack of adequate power analysis

II. We will collect the following data points for retrospective chart review:

a. Recipient: medical record number, transplant date, patient demographics, blood type, End-stage liver disease etiology, Model for end stage liver disease (MELD) score at transplant, end stage renal disease etiology, time of dialysis prior to transplant, CMV status for donor and recipient, Epstein-Barr virus (EBV) status, and post-transplant HCV activation, and post-transplant treatment information

b. Donor: demographics, cause of death, CMV status, EBV status, HCV genotype

III. [] This will also be a descriptive analysis. Continuous variables will be expressed as median and interquartile ranges. Discrete variables will be expressed as percentage. Any p-values will be significant if <0.05

IV. Bibliography

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The Ohio State University Combined Consent to Participate in Research and HIPAA Research Authorization

Study Title: Utilization of Hepatitis C Positive Kidneys in Negative recipients (USE-Hep C)

Principal Investigator: Reem Daloul, MD

Sponsor: None

- **This is a consent form for research participation.** It contains important information about this study and what to expect if you decide to participate. Please consider the information carefully. Feel free to discuss the study with your friends and family and to ask questions before making your decision whether or not to participate.
- **Your participation is voluntary.** You may refuse to participate in this study. If you decide to take part in the study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your usual benefits. Your decision will not affect your future relationship with The Ohio State University. If you are a student or employee at Ohio State, your decision will not affect your grades or employment status.
- **You may or may not benefit as a result of participating in this study.** Also, as explained below, your participation may result in unintended or harmful effects for you that may be minor or may be serious depending on the nature of the research.
- **You will be provided with any new information that develops during the study that may affect your decision whether or not to continue to participate.** If you decide to participate, you will be asked to sign this form and will receive a copy of the form. You are being asked to consider participating in this study for the reasons explained below.

1. Why is this study being done?

You are being invited to participate in a study that aims to evaluate the safety of transplanting hepatitis C virus (HCV) infected kidneys in recipients who have never been infected with HCV. Following transplant, patients will be given very effective medicine to treat the HCV infection.

HCV is one of several viruses that infects the liver. It can be transmitted, or passed, from one person to the other through blood products, sexual contact, or organ transplant. It is estimated that about 3.5 million people in the United States are infected with HCV. There are several types of HCV, called genotypes. These are given the numbers 1 to 6 to name each genotype.

Hepatitis C infection describes the inflammation (redness and swelling) of the liver tissue caused by HCV virus. The disease usually produces no symptoms and many patients do not realize they are infected. The inflammation of the liver usually progresses slowly over the years until it leads to complete scarring of the liver, or what is called “end stage liver disease or cirrhosis”. Concurrent use of anti-rejection drugs can accelerate the damage caused by HCV virus if the virus is not treated or fails to respond to treatment. Patients with end stage liver disease require liver transplant to stay alive.

Previously, kidneys from donors infected with HCV have only been given to patients on the kidney transplant list who also have HCV. This is because the virus passing to the recipient is almost guaranteed. Due to the low number of infected transplant patients, most of the infected kidneys get discarded and go without good use, despite being quality organs. About 800 HCV infected kidneys are wasted each year.

In the last several years, new and highly effective anti-viral drugs, or medicines that treat viral infections, for HCV have become available. These drugs are called direct anti-viral drugs (DAAs), and they inhibit the virus reproduction and can lead to cure of the disease. The cure rate for most of these drugs range between 95-100%. These drugs have made the treatment of HCV infection easy, and they are usually well tolerated by patients. We plan to use these drugs to treat HCV infection after transplanting infected kidneys. We believe this will allow us to decrease the numbers of wasted kidneys and increase the number of patients receiving kidney transplant every year.

The main study drug, Sofosbuvir/Velpatasvir (Epclusa), is FDA approved for treatment of HCV. It is a daily tablet that is given for 12 weeks. The cure rate for Epclusa is between 95-100% and works against all 6 types of HCV. This drug has been used to treat HCV infection in transplant patients and has had a 96% success rate. Epclusa was well tolerated by patients and did not interfere with anti-rejection medications.

Some patients may experience delayed or poor graft function. In these patients, a different anti-HCV drug will be used. Glecaprevir/pibrentasvir (MAVYRET) is given as 3 tablets daily over 12 weeks. The cure rate for Mavyret is also between 95-100% and it is effective against all 6 types of HCV. It has also been shown to be successful in HCV infected transplant patients.

Other FDA approved drugs for treatment of hepatitis C, such as Sofosbuvir/Ledipasvir (Harvoni) or Elbasvir/Grazoprevir (Zepatier), will be used in case your health insurance denies coverage for first and second line therapy.

Patients who have history of hepatitis B virus infection of the liver might have activation of their infection when taking direct anti-viral drugs (DAAs). You will be screened for HBV infection prior to enrollment and will not be enrolled in the study if you tested positive.

If you join the study, you will receive the exact same care you would have received if you decided not to be part of the study. The only difference would be the addition of the study drug and a blood test to monitor for HCV infection called HCV PCR. The blood work for HCV infection will be drawn at the same time you get your routine blood work for transplant. There will be no need for any additional blood testing.

2. How many people will take part in this study?

We plan to enroll 55 patients in this study.

3. What will happen if I take part in this study?

<u>After Enrollment</u>

Once you are enrolled in the study, your status on the kidney waiting system will be changed to “Accepting HCV+ organ”. Once an organ becomes available, it will be offered to you. You have the chance to turn down the offer and withdraw from the study at any point.

After Transplant

After transplant, you will receive the routine care that any other kidney transplant recipient patient normally gets. In addition, we will be monitoring you for HCV infection using a blood test called HCV Polymerase Chain Reaction (PCR). The first check will be on day three post-transplant. If this first test is not positive, you will have blood tests every week for 8 weeks or until the test is positive. If after 8 weeks the test is still negative, we will monitor HCV infection every month until the test is positive or until 12 months is reached.

You will be seen by the Hepatologist (liver doctor) while inpatient and again only if you would become symptomatic.

Once HCV PCR becomes positive, you will start treatment with the anti-viral drug Epclusa (sofosbuvir/velpatasvir). One tab of Epclusa will be taken daily for 12 weeks. At the end of the treatment period, we will repeat the HCV blood test to confirm if the treatment worked. We will repeat the blood test again in the future to confirm the treatment worked and that the infection has not come back. If you have delayed graft function or poor graft function, you will be put on MAVYRET (glecaprevir/pibrentasvir) instead of Epclusa. This drug requires you take 3 tablets daily for 12 weeks. If insurance denies coverage to both of these drugs, you will be treated with either Zepatier (Elbasvir/Grazoprevir) or Harvoni (Sofosbuvir/Ledipasvir). The treatment with either of these two drugs is one tablet daily for 12 weeks. As with Epclusa, blood tests will be repeated to determine whether the treatment worked.

Clinic Follow-up

You will have the same clinic follow-up as other kidney transplant patients. This means you will be seen in clinic every week between weeks 1 and 4, then on weeks 6, 9, and 12 post-transplant. You will then be seen on months 4, 6, 9, and 12 post-transplant.

A table showing the expected schedule of study and clinic activities is shown below.

Activity	Day 0 pre-transplant	Day 3 post-transplant	Wk1	Wk2	Wk3	Wk4	Wk6	Wk9	Wk12	Mo4	Mo6	Mo9	Mo12
Physical examination and blood work(HCV	X												

PCR, Hep B and HIV testing													
Transplant clinic visit			X	X	X	X	X	X	X	X	X	X	X
HCV PCR[a,b]	X	X	X	X	X	X	X		X	X	X	X	X

[a] Patients with a positive HCV PCR at Day 3 post-transplant will receive a follow up HCV PCR on Week 4 and Week 12 of therapy.

[b] Patients with a negative HCV PCR prior to discharge will have an HCV PCR checked weekly for 8 weeks, then monthly until Month 12.

What Are Your Responsibilities During The Study?

In order for this study to provide good information about how the study drugs work, you will be asked to do the following:

- Take all study drugs with food and as directed by your study doctor.
- Follow the instructions of your study doctor including requirements to use appropriate birth control methods.
- Come to all your scheduled visits and procedures. Let your study doctor know as soon as possible if you are not able to attend a visit so that they can work with you to make other arrangements.
- Review all the medications you are taking with your study doctor. You may have to stop or adjust the dose of certain medications and supplements before or during the study.
- Do not change, start or stop any medications without checking first with your study doctor.
- Tell the study staff what medical procedures/conditions you have had in the past. Some procedures/conditions you may have had in the past may keep you from being in this study.
- Tell the study staff about any health problems or side affects you are having even if you don't think they are important or related to the study drugs or if you have made any visits to other doctors or hospitals.
- Tell the study staff if you wish to stop being in the study.
- Do not participate in any other research studies during your participation in this study.
- Avoid drinking alcohol for at least 6 months post-transplant.
- In the event of an emergency, dial your local emergency phone number immediately.
- If you require emergency care, be sure to tell the emergency care provider about your participation in this study. Contact the study doctor or study staff as soon as possible

Study Drug Instructions:

- You will receive specific instructions on how to take all of the study drugs. You will have a discussion with your study doctor or staff about the importance of taking your study drugs with food and at the same time each day. Should you miss taking a dose at a scheduled time, it is important that you tell your study doctor at your next visit. If you decide to stop taking your study drugs, it is very important that you tell your study doctor right away.
- Take and store your study drug as instructed and return the unused study drug and/or empty containers to the study doctor's office at each visit. Do not share your study drug with anyone. You are the only person allowed to take the study drug. Keep the study drug and study supplies out of the reach of children and persons of limited ability to read or understand

4. How long will I be in the study?

It is difficult to say exactly how long you will be in this study since we do not know how long it will take for a donor organ to become available once your status is changed with UNOS (United Network for Organ Sharing). However, you will be in the study for up to 1 year following your transplant. It is estimated that the maximum amount of time you will dedicate to study specific visits is 5 hours over this 1 year period. This is based on need for study initiation visit (about 20-30 minutes including time for blood draw), post-transplant HCV blood tests (variable numbers. A total of 5-6 HCV blood test post-transplant is expected in 99% of the patients. Less than 1% of the patients might need more frequent HCV tests, up to a maximum of 21 tests) and any applicable Hepatology clinic visits (approximately 30 minutes each). Your exact time commitment will be dependent on how long it takes for you to have a positive HCV result and whether you require a second round of HCV treatment. When possible, blood draws will be done at the same time as regular transplant visits to minimize extra time commitment.

5. Can I stop being in the study?

You may leave the study at any time. If you decide to stop participating in the study, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled. Your decision will not affect your future relationship with The Ohio State University. If you leave the study before transplant, you can be listed back the deceased

waiting list. Your participation in the study will not affect in any way your position on the deceased waiting list.

While you can leave the study at any time, stopping study drugs before the study drug has been completed can reduce the chance that the HCV infection will be successfully cured. In addition, stopping study medication before the treatment has been completed might increase the chance that your HCV will develop resistance to one or all of these drugs. It is possible that virus with resistance to these drugs may also be more difficult to treat in the future with other anti HCV drugs.

6. What risks, side effects or discomforts can I expect from being in the study?

Risk of contracting HCV

The main risk associated with this study is becoming infected with HCV. The likelihood that you will get this infection from the donor is close to 100%. However, we will monitor your blood for signs of infection very closely and we will start treatment with the anti-viral as soon as we discover the earliest sign of infection. The cure rate with any of the anti-viral drugs is more than 95%. There is a very small chance (less than 5%) that you will not be cured after the first round of treatment. In this case, a second round (another 12 weeks for Epclusa or Mavyret) of treatment will be needed. Most patients will be infection free after 1 or 2 treatment rounds. If you fail to clear the infection, you might develop severe liver disease.

There is a risk that your HCV may become resistant to the specific study drug you are treated with during this study. The risk that your HCV will develop resistance is unknown. It is also not known how long HCV might remain resistant to the specific drug after you stop taking it. Resistance to one study drug may lead to resistance to other anti-HCV drugs called DAAs, similar to the ones taken in this study, and this could affect your response to treatment with DAAs in the future. During the course of this study, you will be monitored for the development of resistance.

If you are infected with HCV, there is the risk of you passing this infection to the people you contact. HCV is believed to be most efficiently passed from the blood of one person to the blood of another. Following your transplant, care should be taken to not share items that may have blood on them (e.g. razorblades, toothbrushes, needles) and to keep open cuts or wounds properly covered. Although rare, HCV can also be passed through sexual contact. Sexual contact that includes contact with blood of an infected individual increases the likelihood of the virus being passed.

Risks of the Epclusa, MAVYRET, Harvoni, Zepatier

The most common side effects experienced following treatment with one of the DAAs (more than 10% of patients) were: fatigue, headache, and nausea. Less commonly experienced side effects include insomnia, irritability, cough, skin rash, and indigestion.

Sometimes people have allergic reactions to these drugs. In extreme cases, an allergic reaction may lead to death. Some symptoms of a life-threatening allergic reaction (anaphylaxis) are:

- A rash
- Difficulty breathing
- Wheezing
- A sudden drop in blood pressure. (making you feel dizzy or lightheaded)
- Swelling around the mouth, throat, or eyes
- A fast pulse
- Sweating

You should get immediate medical attention if you experience any of these signs of a serious allergic reaction. If you experience any side effects during the study, please contact the study doctor or staff to report what you are experiencing.

Reproductive risks

Studies conducted in animal showed that Epclusa did not result in harmful effects to the fetus. However, such studies have not be conducted in humans and hence the effect of Epclusa in pregnancy is not known.

Additionally, anti-rejection medications are known to have risks of first trimester pregnancy loss and congenital malformation.

Females:

If you are a sexually active female able to have children, you must use two forms of contraception simultaneously unless complete abstinence from heterosexual intercourse is your chosen method. The study doctor must approve the methods of birth control that you will be using and you must agree to continue using those methods of birth control following completion of the study.

Medically proven methods of birth control can include oral or implanted hormonal contraceptives like the pill, barrier methods (e.g., condom with spermicide, diaphragm or vaginal cap with spermicide), or sexual abstinence. If you are a woman and have been surgically sterilized or you are in menopause (at least 12 consecutive months without menses) you do not need to use contraceptive methods.

In case you discontinue study drug but continue taking mycophenolate mofetil (MMF), a medicine used to weaken your immune system so you do not reject your new organ, you must continue using adequate contraception.

Males:

Unless you have a previous history of vasectomy, you must agree to consistently use a condom during heterosexual interaction. In addition, you must agree not to donate sperm from Study Day 1 through 7 months after the last dose of study drug

Loss of Confidentiality

Any time data is collected on a participant, there is the risk this information may be accessed by someone outside of the study. All precautions will be taken to avoid loss of confidentiality such as storing information in a locked office, on a protected computer and secure network. Any loose paper containing participant information will be stored in a locked office and locked cabinet. Only study personnel will have access to this information.

Study drug interactions

It is possible that taking the study drugs with your regular medications or supplements may change how the study drugs, your regular medications (such as atorvastatin, Prilosec, warfarin, colchicine and amiodarone), or your regular supplements work. It is very important that you tell the study doctor about all medications or supplements you are taking during the study including those you take as needed or which you take only occasionally. Your medication list will be reviewed during each clinic visit to confirm there is no dangerous or significant drug-drug interaction.

If you stop or change your regular medication to be in the study, your health might get worse. Please tell the study doctor or study staff right away if you have any problems when you stop taking or change your regular medication.

7. What benefits can I expect from being in the study?

If you decide to join the study, you will be listed on the HCV positive kidney waiting list. The wait time on this list is much shorter, usually between 3-6 months compared to 2-5 years on the regular kidney waiting list. Additionally, donors who have HCV infection are usually younger and otherwise healthier. This means the quality of the organ is usually, though not always, better than average.

8. What other choices do I have if I do not take part in the study?

You may choose not to participate without penalty or loss of benefits to which you are otherwise entitled. You do not have to participate in this study to receive kidney transplant.

Your study doctor can discuss the risks and advantages of alternative treatment methods with you.

9. What are the costs of taking part in this study?

The transplant and your regular post-transplant treatment are standard of care and will not be covered by this study. You or your insurance company will be billed for the transplant surgery and any standard of care clinic visits. You will be responsible for any out of pocket expenses associated with your insurance plan. In the unlikely event you incur unexpected costs related to therapy, the study team will work with you to help cover the costs.

10. Will I be paid for taking part in this study?

Participation in the study is completely voluntary. There will not be any financial reimbursement or incentives to being part of the study.

11. What happens if I am injured because I took part in this study?

If you suffer an injury from participating in this study, you should notify the researcher or study doctor immediately, who will determine if you should obtain medical treatment at The Ohio State University Wexner Medical Center.

The cost for this treatment will be billed to you or your medical or hospital insurance. The Ohio State University has no funds set aside for the payment of health care expenses for this study.

12. What are my rights if I take part in this study?

If you choose to participate in the study, you may discontinue participation at any time without penalty or loss of benefits. By signing this form, you do not give up any personal legal rights you may have as a participant in this study.

You will be provided with any new information that develops during the course of the research that may affect your decision whether or not to continue participation in the study.

You may refuse to participate in this study without penalty or loss of benefits to which you are otherwise entitled.

An Institutional Review Board responsible for human subjects research at The Ohio State University reviewed this research project and found it to be acceptable, according to applicable state and federal regulations and University policies designed to protect the rights and welfare of participants in research.

13. Will my study-related information be kept confidential?

Efforts will be made to keep your study-related information confidential. However, there may be circumstances where this information must be released. For example, personal information regarding your participation in this study may be disclosed if required by state law.

Also, your records may be reviewed by the following groups (as applicable to the research):

- Office for Human Research Protections or other federal, state, or international regulatory agencies;
- U.S. Food and Drug Administration;
- The Ohio State University Institutional Review Board or Office of Responsible Research Practices;
- The sponsor supporting the study, their agents or study monitors; and
- Your insurance company (if charges are billed to insurance).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search the website at any time.

14. HIPAA AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

I. What information may be used and given to others?

- Past and present medical records;
- Research records;
- Records about phone calls made as part of this research;
- Records about your study visits;
- Information that includes personal identifiers, such as your name, or a number associated with you as an individual;
- Information gathered for this research about:

  HIV / AIDS

  Hepatitis infection

  Sexually transmitted diseases

  Other reportable infectious diseases

  Physical exams

  Laboratory, x-ray, and other test results

- Records about any study drug you received;

II. Who may use and give out information about you?

Researchers and study staff.

III. Who might get this information?

- The sponsor of this research. "Sponsor" means any persons or companies that are:
  - working for or with the sponsor; or
  - owned by the sponsor.
- Authorized Ohio State University staff not involved in the study may be aware that you are participating in a research study and have access to your information;
- If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic or physician's office record;

IV. Your information <u>may</u> be given to:

- The U.S. Food and Drug Administration (FDA), Department of Health and Human Services (DHHS) agencies, and other federal and state entities;

- Governmental agencies in other countries;
- Governmental agencies to whom certain diseases (reportable diseases) must be reported; and
- The Ohio State University units involved in managing and approving the research study including the Office of Research and the Office of Responsible Research Practices.

V. Why will this information be used and/or given to others?

- To do the research;
- To study the results; and
- To make sure that the research was done right.

VI. When will my permission end?

There is no date at which your permission ends. Your information will be used indefinitely. This is because the information used and created during the study may be analyzed for many years, and it is not possible to know when this will be complete.

VII. May I withdraw or revoke (cancel) my permission?

Yes. Your authorization will be good for the time period indicated above unless you change your mind and revoke it in writing. You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the researchers. If you withdraw your permission, you will not be able to stay in this study. When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

VIII. What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study and receive research-related treatment. However, if you are being treated as a patient here, you will still be able to receive care.

IX. Is my health information protected after it has been given to others?

There is a risk that your information will be given to others without your permission. Any information that is shared may no longer be protected by federal privacy rules.

X. May I review or copy my information?

Signing this authorization also means that you may not be able to see or copy your study-related information until the study is completed.

15. Who can answer my questions about the study?

For questions, concerns, or complaints about the study, or if you feel you have been harmed as a result of study participation, you may contact ***Dr. Reem Daloul at ____reem.daloul@osumc.edu_____***.

For questions related to your privacy rights under HIPAA or related to this research authorization, please contact ***HIPAA Privacy Officer, Suite E2140, 600 Ackerman Road, Columbus, OH 43201***.

For questions about your rights as a participant in this study or to discuss other study-related concerns or complaints with someone who is not part of the research team, you may contact Ms. Sandra Meadows in the Office of Responsible Research Practices at 1-800-678-6251.

If you are injured as a result of participating in this study or for questions about a study-related injury, you may contact ***Dr. Reem Daloul at_____reem.daloul@osumc.edu_____***.

Signing the consent form

I have read (or someone has read to me) this form and I am aware that I am being asked to participate in a research study. I have had the opportunity to ask questions and have had them answered to my satisfaction. I voluntarily agree to participate in this study.

I am not giving up any legal rights by signing this form. I will be given a copy of this combined consent and HIPAA research authorization form**.**

Printed name of subject	**Signature of subject**
	AM/PM
	Date and time
Printed name of person authorized to consent for subject (when applicable)	**Signature of person authorized to consent for subject (when applicable)**
	AM/PM
Relationship to the subject	**Date and time**

Investigator/Research Staff

I have explained the research to the participant or his/her representative before requesting the signature(s) above. There are no blanks in this document. A copy of this form has been given to the participant or his/her representative.

Printed name of person obtaining consent	Signature of person obtaining consent
	AM/PM
	Date and time

Witness(es) - *May be left blank if not required by the IRB*

Printed name of witness	Signature of witness
	AM/PM
	Date and time

Printed name of witness	Signature of witness
	AM/PM
	Date and time