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TITLE:

Development and validation of a shared-decision making tool for initiation of treatment in patients with Hepatitis C infection and chronic kidney disease

Project HELP (**H**elping **E**mpower **L**iver and kidney **P**atients)

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WASHINGTON UNIVERSITY'S IRB

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List of Abbreviations

CKD	*Chronic Kidney Disease*
DA	*Decision Aid*
DAAs	*Direct Acting Antivirals*
eGFR	*estimated Glomerular Filtration Rate*
HCV	*Hepatitis C Virus*
HELP	*Helping Empower Liver and kidney Patients*
IRB	*Institutional Review Board*
ODSF	*Ottawa Decision Support Framework*
PASS	*Power Analysis and Sample Size Software*
SVR	*Sustained Virologic Response*
SOP	*Standard Operating Procedure*

1 Background and Rationale

1.1 Background

Hepatitis C virus (HCV) infection is a chronic, debilitating disease that affects 170 million people globally and about 3.9 million people in the U.S. [1]. HCV infection is the most common blood-borne illness in the U.S [2], and is especially prevalent among those with chronic kidney disease (CKD). The estimated prevalence of HCV in hemodialysis patients in the U.S. is 8% [3], almost five times greater than the prevalence in the general US population [4]. Some individuals with untreated HCV can develop serious complications including cirrhosis, liver failure, and/or hepatocellular carcinoma [5].

Among patients with CKD, the presence of HCV can significantly impact both quality of life and health outcomes. Patients with CKD who are HCV+ may have an increased risk of death, loss of kidney function, and kidney transplant failure [5-11]. HCV infection has been linked with lower quality of life in patients on dialysis, and may be particularly detrimental to patients' mental health [12].

The goal of therapy for chronic HCV infection is a sustained virologic response (SVR) where the disease is no longer detected for six months (24 weeks) following discontinuation of therapy [13]. SVR reduces the likelihood of cirrhosis of the liver, liver cancer, the need for liver transplantation and overall death rates among patients with CKD [14-17]. As a result, national and international guidelines suggest that HCV+ patients with CKD should consider anti-viral treatment for their HCV [18].

Despite these potential benefits, few patients with CKD receive treatment for their HCV infection [19]. Early medications for HCV infection included interferon, Pegylated interferon and/or ribavirin as treatment options available for HCV infected patients. These drugs were not always effective, eliminating HCV from only 14%-63% of patients [20]. Furthermore, many patients experienced serious side effects from treatment and reduced their doses or discontinued treatment on these medications [21, 22]. Because these drugs are renally eliminated, treating HCV in CKD patients was especially challenging, and many patients with CKD and their clinicians felt that the potential benefits of treatment did not outweigh the potential risks. As a result, as few as 1% of HCV+ CKD patients were prescribed antiviral medications [2].

In recent years, direct-acting antivirals (DAAs) specifically designed to attack HCV proteins were developed and became available as treatment options for patients with HCV infection. DAAs have a much higher SVR (>95%) and relatively few toxicities compared to earlier treatments [23, 24]. They also have easier dosing regimens and fewer interactions with other medications used to treat patients with comorbidities [24]. Studies suggest that patients with mild to moderate renal impairment tolerate treatment with DAAs well, and have many positive outcomes from these treatments. However, they may face complicated decisions about whether to consider pre-emptive kidney transplants or other treatments before or after treating their HCV.

In addition, some patients with significant renal impairment (eGFR <30) and comorbidities, decisions about whether and when to treat HCV are complex. Factors such as patients' CKD severity, genotype, transplant status (e.g., on-waiting list for kidney transplant, which can lead to

decisions about whether treatment will delay kidney transplant), and comorbidity status can influence treatment decisions and outcomes. Patients' subjective preferences for the tradeoffs between potential benefits and harms of treatment can significantly impact choices. Patients' insurance coverage and potential out-of-pocket costs can also impact their access and adherence to treatment [3] [4]. In order to make treatment decisions, patients must balance each of these factors, as well as advice from multiple clinicians, including nephrologists, hepatologists, and sometimes a primary care provider.

Given the variety and complexity of treatment options that depend on patients' clinical characteristics and personal preferences, interventions are needed to better prepare patients to discuss options with clinicians. Patient decision aids (DAs) are designed to help patients understand complex health options and take an active role in decision-making. DAs differ from education materials because of their detailed, specific, and personalized focus on options, outcomes, probabilities, and patients' values. DAs have been shown to reduce decisional conflict, increase patient's knowledge of treatment options, lower decision regret, increase patient involvement in decisions, reduce patient indecision concerning treatment, and increase the probability that treatment decisions will be consistent with patients' values [25].

1.2 Rationale

This project has the potential to improve clinical practice in several ways. We will be addressing a critical decision that patients and clinicians face about treatment options among patients with HCV and CKD. Current available evidence is inadequate to suggest one dominant treatment plan. Our project will help patients and clinicians weigh the evidence and consider patients' preferences to support patients through this complex decision. To our knowledge, there is limited literature on ways to support patients' decisions about this topic and no available decision tool to facilitate this process.

In addition, our project will incorporate physician and patient stakeholder input in the design of the DA such that the decision incorporates patients' preferences and clinical characteristics that impact outcomes. We will pilot test it to demonstrate its effect on decision quality. This process of gaining stakeholder input from individuals outside the development process and pilot testing it with patients is consistent with international guidelines for decision aid development [26], and ensures that our tool is relevant to end users.

Finally, there is variation in how clinicians approach this decision about whether and when to treat HCV among advanced CKD patients. A successful DA could be disseminated in a future study to help incorporate patient preferences into this decision across regions. Including stakeholders from different geographic regions makes our project more suitable for wider scale dissemination, and it will be adaptable for various clinics.

2 Objectives

Aim 1: To develop a decision aid (DA) for patients with Hepatitis C virus and chronic kidney disease to support their decisions about whether, when, and how to treat each illness.

Aim 2: To pilot test the DA to determine its efficacy, usability, and likelihood of using it in routine practice

3 Methodology

3.1 Summary of Study Design

Aim 1 Methods:

DA Content and Structure: Drs. Politi, Li, and Korenblat will draft the DA based on literature reviews and guidance from the expert advisory group. The expert advisory group will consist of 2 external nephrologists (Dr. David Roth and Dr. Jerry Yee), 2 external hepatologists (Dr. AnnMarie Liapakis and Dr. Chanda Ho) and 2 patients (Mr. Kevin Fowler and Mr. John Terry). First, we will begin with a knowledge section. It will include a basic overview of HCV, CKD, and treatment options for HCV among this population (see table 1 for examples of possible content, to be edited with input from the expert advisory group, designed according to International Patient Decision Aids Standards).

Table 1. Tabs/Headings of Content for Project HELP Decision Aid Tool

Navigation Tabs	Page Headings	Sub Headings/Description
Welcome		An introductory page which explains the purpose of the tool, its developers and funder.
Let's Learn	Hepatitis C	What is Hepatitis C? What are the health effects of Hepatitis C?
	Chronic Kidney Disease	What is chronic kidney disease? What are the health effects of chronic kidney disease? What can I do to keep my kidneys healthy as long as possible?
	Treating Hepatitis C and Chronic Kidney Disease	What is the relation between Hepatitis C and Chronic Kidney Disease? How does having Hepatitis C and Chronic Kidney Disease affect my Hepatitis C treatment choices? What choices should I discuss with my doctor?
Let's Review		8 review questions asked based upon the content the patient reviewed
Let's Explore What Matters to You		7 questions about what matters to the patient when it comes to treating their illnesses (CKD and HCV).
Summary Page		A summary page of the information the patient input in the tool.

We will base our preliminary content of the DA on the Kidney Disease International Guidelines (KDIGO), the American Association for the Study of Liver Disease with Infectious Disease Society of America (combined guidelines and graded evidence), and our advisory board feedback. Benefits and risks for options will be presented according to the latest standards in risk communication [31-33]. References will be listed for those who want additional information. The DA will be written at an 8th grade reading level or below as assessed by the Flesch–Kincaid readability test.

Next, the DA will assess individual factors that could impact HCV and CKD outcomes (e.g., comorbidities, CKD severity, stage of fibrosis, and genotype). The tool will provide personalized

and tailored feedback to patients about these outcomes. The message library and algorithms will be drafted by Drs. Politi and Li.

After providing personalized risk information, the DA will include a values clarification component. Values clarification (exploring patient preferences) is an integral part of DAs [34]. In order to understand how decisions about HCV are made among patients with advanced CKD, it is important to understand how individuals weigh the factors they are considering in their decision making. We will incorporate an interactive balance scale that lists the pros and cons of each option, allowing the user to attach his/her own values and ratings to each potential outcome. Items on the rating scale will be programed so that patient can slide a button to show the correct number that shows their answer. For example, we might ask the following question:

"How worried are you about side effects of the drugs used to treat your Hepatitis C?"

Not at all worried				*Very worried*
1	*2*	*3*	*4*	*5*
O	*O*	*O*	*O*	*O*

The DA will then include a section where patients can list questions for their clinicians to facilitate a conversation about the decision. This part of the DA will allow treating clinicians to review information the patient has considered, and to personalize the discussion to the patient's clinical context and preferences. For example (questions not comprehensive, just selected examples; content and questions will be created and reviewed by the expert advisory board):

*"**What should I ask my doctor about treating kidney disease and Hepatitis C?***
Some people have questions that can affect their treatment choice. Here are some common questions people have.

1. *What are the pros and cons of treating my Hepatitis C?*
2. *How will treating my Hepatitis C affect my quality of life?*
3. *How can I keep my kidneys healthy as long as possible?*
4. *Should I consider a pre-emptive kidney transplant? If so, when?*
5. *Add your own question here:* _____

_____

_____

We will make the DA available to complete via tablet PCs at the clinic to reduce bias in recruiting patients who are familiar with computers and the Internet. However, patients who want to see the information on paper can opt to do so given the age of this population and variations in comfort using computers. Patients will be able to review the DA content at any point, and can take home a printed summary of the information so that they can review a summary with caregivers and/or their clinician. The summary will also be placed in their medical chart so that the clinicians can use it to personalize discussions. We will work with our patient and clinician stakeholders to identify when the optimal timing will be for patients to complete this tool without disrupting clinic flow. We will conduct informal usability testing with 10 additional patients to ensure that wording and formatting is clear to patients. These patients will not be included in Aim 2 so as not to bias Aim 2 participants.

Aim 2 Methods: The goal of Aim 2 is to pilot test the DA to determine its efficacy and the likelihood of using it in routine practice. We will pilot this with 70 patients using a within subjects design. Outcomes will include change in decisional conflict, change in decision self-efficacy, change in knowledge about HCV treatment risks and benefits among patient with CKD, and the match between patients' intended choice and their preferences.

A quasi-experimental design was chosen to examine within group (pre-post use of the DA) outcomes. We considered conducting a randomized trial. However, randomizing individual patients or clinicians might lead to an underestimation of the effect of the DA, as the DA would likely contaminate standard procedures. Moreover, given the size and scope of this pilot project, our goal is to demonstrate feasibility and preliminary efficacy which can be accomplished at our institution through a within subjects design.

3.2 Study Population

There will 100 participants recruited for the study in total. Of the total study population, 70 participants will be a part of aim 2 of our study and the remaining 30 participants will be participating in aim 3. For aim 2, patients will be recruited beginning November 2017 and lasting for 7 months. There are approximately 2600 patients in our CKD clinic (1552 with eGFR < 60, 560 with eGFR < 30) and over 500 dialysis patients. We also follow renal transplant patients in a transplant clinic. About 300 of these patients also have HCV. Based on these numbers, recruiting 70 patients in this time frame is feasible and can provide us with pilot data to evaluate our decision tool prior to a future randomized trial assessing effectiveness of the tool on clinical decision-making.

3.3 Inclusion Criteria

Aim 2 - Eligibility Criteria:

- Over the age of 18
- English-speaking
- Have HCV infection of any genotype
- And a diagnosis of CKD (we will stratify by GFR <30 and GFR >30).

3.4 Exclusion Criteria

Exclusion criteria include:

- Patients with self-reported or observed unstable medical or psychiatric condition, which would preclude providing consent or participating in the study
- Patients with any of the following:
    - Decompensated cirrhosis
    - Hepatocellular carcinoma
    - Post-liver transplantation

4 Variables and Measurement

4.1 Study Outcomes

• ***Knowledge:*** Similar to knowledge items used when designing DAs[37-39] and assessing decision quality[40], we will develop knowledge items based on information that is considered essential to making treatment decisions (e.g. understanding terms, understanding facts that differentiate options)[41]. Questions will be asked using true/ false/ unsure responses. Total number of correct responses to the items will be calculated. One point will be given for each correct response and zero for unsure or incorrect responses; answers will be expressed as percent correct. Similar scales have been used in other DA trials [38, 39] and have good internal consistency (Cronbach's alpha coefficients range from 0.82 – 0.83) [37].

Decisional Conflict: The Decisional Conflict Scale [42] (DCS) is a validated and widely-used measure of uncertainty about decisions. We will administer the 4-item SURE Test version of the DCS [42] to assess whether individuals feel they have enough information to make a choice, are clear about their values for risks and benefits of their choice, and feel they have enough support to make a choice. Items are scored as 1 (yes) or 0 (no). If the total score is less than 4, it indicates the probability that a patient experiences clinically significant decisional conflict.

• ***Decision Self-Efficacy*****:** We will use the lower literacy version of the Decision Self-Efficacy Scale [43], a validated measure of an individual's self-confidence or belief in their ability to make a decision. Individuals are asked to rate on a three-item scale how confident they feel taking actions involved in making an informed choice (e.g., gathering information, asking questions, and expressing opinions). This scale has been validated and used to study health literacy and shared decision making among patients and lower SES populations among others [43-46]. It has high levels of internal consistency (mean Cronbach's alpha = 0.86) [43] and correlates with feeling informed, supported, and knowledgeable about decisions [43].

• ***Usability:*** After participants use the DA, they will complete the 10-item System Usability Scale (SUS [47]) to measure the DA's usability. We will also ask clinicians to fill out this measure after the end of the study.

4.2 Covariates Measured

At this time, planned covariates for the multivariate model include age and stage of fibrosis. For the model for which knowledge is the primary outcome, we will also control for health literacy. We will collect the following additional measures:

- ***Clinical Characteristics:*** We will document stage of kidney disease, stage of fibrosis, genotype of Hepatitis C, prior treatment history for Hepatitis C, time since Hepatitis C infection, and comorbidities.

• ***Demographics:*** We will explore whether any demographic variables (age, education, gender, race, insurance status) influence outcomes, controlling for significant covariates in the analysis.

• ***Health Literacy:*** We will control for health literacy in our analysis of the effect of our DA on knowledge. Participants will complete the Rapid Estimate of Adult Literacy in Medicine-Short Form [48].

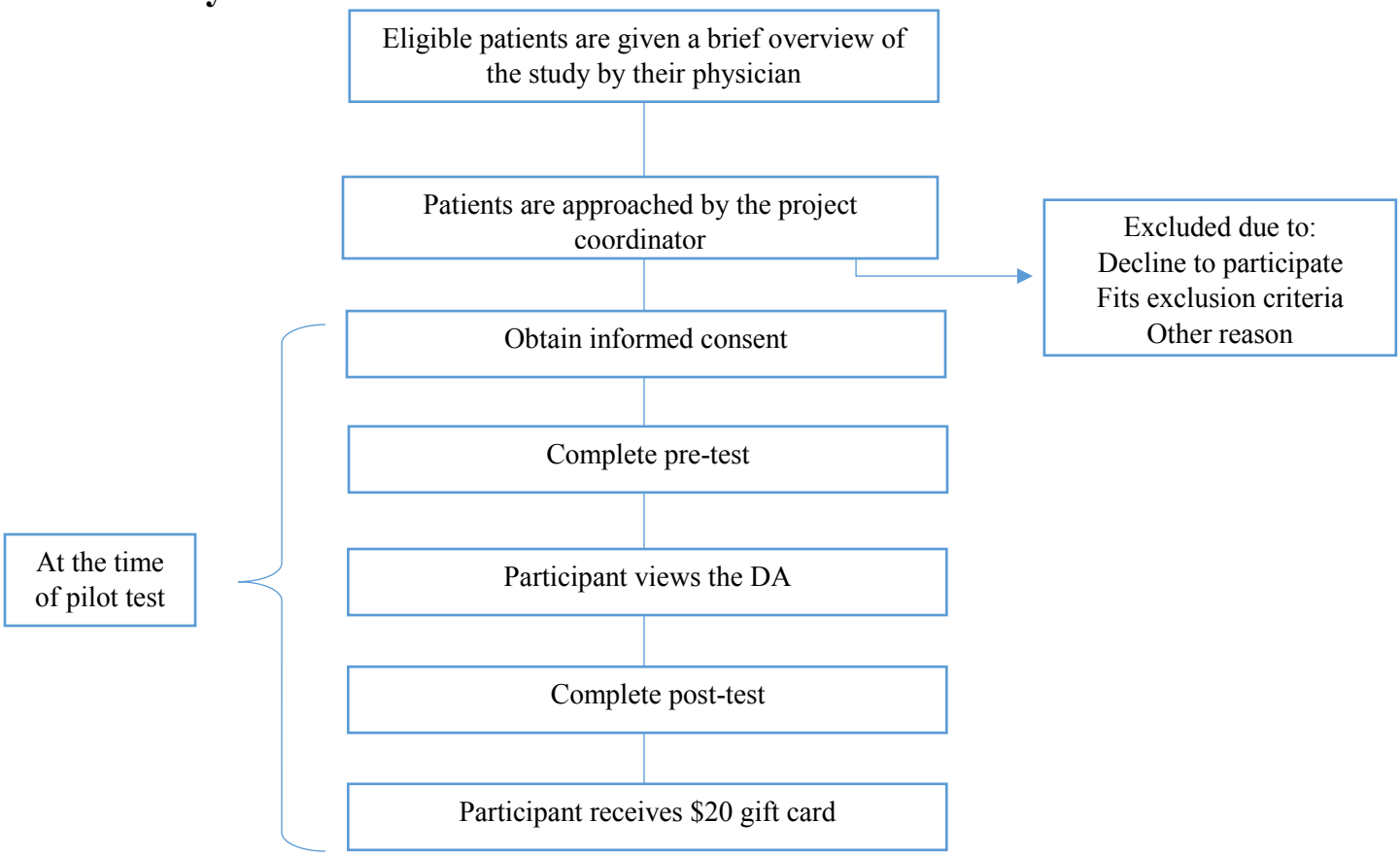
• ***Preferred Decision Role:*** We will use The Control Preference Scale [49, 50] to assess the degree of involvement patients prefer in their medical decisions. Patients are asked to select one of five statements that best reflects their preference for decision control from active to collaborative to passive roles in treatment decision making.

4.3 Exploratory Analysis

• **Match between values and choice:** We will explore patients' values (as assessed in the decision tool by sliding a bar to indicate what is important to them) and their post-tool treatment choice for treating HCV and CKD, if they are leaning towards a choice. We will document whether their values match the choice they are selecting with their provider. This analysis will be completed after the tool and will be descriptive only, as we will not have a control group for comparison. However, it will be important to document their values and choice to indicate what percentage of patients who complete the tool select a treatment that matches their values. Future larger studies evaluating the tool could then explore the role of the decision tool in supporting patients to choose treatments aligned with their values.

• **Financial Toxicity:** We will ask patients about how much treatment costs (e.g., copayments, out-of-pocket costs prior to reaching deductibles) impact their choices using items from a financial toxicity measure previously developed in the context of cancer. We will explore whether patients leaning toward different choices report different levels of financial toxicity.

5 Study Flow Chart



6 STUDY PROCEDURES

6.1 Study Procedures

The Study Diagram in Section 5 summarizes the study procedures to be performed at each visit. Individual study procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator. Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor for reasons related to subject safety.

6.1.1 Administrative Procedures

6.1.1.1 Recruitment and Procedures

Aim 2- The goal of Aim 2 is to pilot test the DA to determine its efficacy and the likelihood of using it in routine practice**.** Eligible patients will be determined by the outpatient EMR (AllScripts). Once patients have been identified, their hepatologist or nephrologist will briefly describe the project and gauge patients' interest in participating. The project coordinator will then reach out to interested patients to describe the project in further detail and obtain informed consent. Patients will complete a brief pre-test questionnaire assessing socio-demographics, health literacy, knowledge, decisional conflict, and decision self-efficacy. All measures were chosen based on their short length so as not to burden participants. We have used a similar recruitment strategy and measures in past projects, and the procedures did not disrupt patient flow or introduce burden on patients [35, 36]. We will document CKD stage, dialysis status (yes/no), stage of fibrosis of the liver, whether or not the patient has tried using a DAA in the past to treat HCV, and presence of comorbidities (diabetes, heart disease, high blood pressure, HIV) to use for tailoring health information in the decision tool. This information will be collected from patients and clinicians and verified in the medical record with patients' consent.

Next, we will provide patients with the DA through tablet PCs on-site, brief training on how to use the tablets, and we will allow patients to view the DA. Patients can opt to view it on paper if they are uncomfortable with computers. They can take home a printed summary of the information to review at home before meeting with their clinician. The summary will also be placed in the patient's chart. After viewing the DA, patients will complete post-test measures of knowledge, decisional conflict, and decision self-efficacy. Recruitment will occur over 12 months. Patients will be provided with a $20 gift card for participation and will have the added benefit of using the DA. We anticipate the pilot test to take about 30-45 minutes.

6.1.1.2 Informed Consent

Before subjects participate in the study, the project purpose and risks will be described by the research coordinator. Any questions participants have will be answered, and informed consent will be obtained. Informed consent will be obtained from each individual prior to their participation in the study. The consent form will cover the subjects most relevant to participants, including the purpose of the study, the institution conducting the research, sponsor of the study, length of the study, the risks and benefits of the study, and the confidentiality protections to be in

place. The research coordinator will ensure that subject understand that their participation is completely voluntary and that they can withdraw at any time without penalty. Participants will also be provided with the contact information of a research team member who can provide additional information about the study. We will ensure that the consent document states that this tool does not replace a conversation with a provider and is intended to be used to prepare patients for conversations with providers.

Consent will be documented by the participant's dated signature or legally acceptable representative's dated signature on an IRB-approved consent form, along with the dated signature of the person conducting the consent discussion. A copy of the signed and dated consent form will be given to the subject before participation in the study.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

The informed consent will adhere to Washington University's Human Research Protection Office requirements, and will adhere to applicable laws and regulations and Sponsor requirements.

7 Safety Reporting and Related Procedures

Introduction

This is a primary data collection non-interventional study being conducted within routine medical practice. All direction for medication usage is at the discretion of a physician in accordance with usual medical practice. No administration of any therapeutic or prophylactic agent is required in this protocol, and there are no procedures required as part of this protocol.

7.1 Adverse Event Reporting

7.1.1 INVESTIGATOR RESPONSIBILITY

If the investigator becomes aware of any serious adverse event (SAE), including death due to any cause, or non-serious adverse reaction (NSAR) following the use of any Merck product, the event must be reported according to Table 1. The investigator must evaluate each SAE for causality and record causality on the AE form for each event reported.

Similarly, pre-specified Health Outcomes of Interest (HOIs) that meet criteria for SAE/NSAR, special situations, and any spontaneously reported AEs must be reported according to Table 1.

Table 1: AE Reporting Timeframes and Process for Investigators and Vendors

EVENT TYPE	**INVESTIGATOR TIMEFRAME**	**VENDOR TIMEFRAME**
	Investigator to Vendor [1], [2] OR Investigator to Merck [3]	**Vendor to Merck [4]**
SAE, regardless of causality (primary data collection) Serious pre-specified HOI Serious Special Situation, regardless of causality	24 hours from receipt	2 BD/3 CD from time of receipt from investigator
NSAR Non-Serious pre-specified HOI if NSAR Non-serious Special Situation, regardless of causality	10 CD from receipt	10 CD from time of receipt from investigator
Spontaneously reported adverse events for Merck products-submit using above timeframes		
If the investigator elects to submit AEs for **non-Merck products**, they should be reported to the market authorization holder (MAH) for that product or to the health authority according to the institution's policy or local laws and regulations. Note: Per **[2],** below, AEs for comparators must be entered in study database.		
Follow-up to any event-submit using above timeframes		

BD-Business Day; CD-Calendar Day
[1] AE reports from investigators must be transmitted via fax, secure email (if available), or entered directly into vendor's electronic data collection (EDC) platform, if utilized. **[2] Investigator to Vendor**: Applies to events for **Merck study product**, **non-Merck comparators**, and ***other*** **Merck products** when a VENDOR is managing AE reporting from investigator to Merck. Events for **Merck study product** and **non-Merck comparators** are entered in study database for tabulation in study report. Events for ***other*** **Merck products** are *not entered in study database* but must be forwarded to Merck for regulatory reporting. **[3] Investigator to Merck:** Applies to studies that do not have a vendor managing AEs. **[4] Vendor to Merck:** Applies to events for **Merck study product** and ***other*** **Merck products** if the vendor is managing AE reporting between investigator and Merck. Not applicable for studies not using a vendor for AE reporting.

Submitting AE reports to Merck Global Safety: All AEs must be submitted to AER Mailbox FAX #215-661-6229 **(US), or toll-free fax 1-800-547-5552 (ex-US and US availability), in English using an AE form (attached) for reporting to worldwide regulatory agencies as appropriate.**

7.2 DEFINITIONS

7.2.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered sponsor's product and which does not necessarily have to have a causal relationship with this product. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the product, whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the product, is also an adverse event.

7.2.2 Adverse Reaction (AR); also referred to as Adverse Drug Reaction (ADR)

An AE which has a causal relationship with the product, that is, a causal relationship between the product and the adverse event is at least a reasonable possibility.

7.2.3 Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that results in death, is life threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, is a congenital anomaly/birth defect, or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered an SAE/SAR when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

7.2.4 Non-serious Adverse Reaction (NSAR)

An adverse reaction that does not meet any of the serious criteria in 7.2.3.

7.2.5 Special Situations

The following special situations are considered important safety information and must be reported, regardless of seriousness or causality, if the investigator becomes aware of them:

- Overdose
- Exposure to product during pregnancy or lactation
- Lack of therapeutic effect
- Off-label use, medication error, misuse, abuse, or occupational exposure
- Suspected transmission via a medicinal product of an infectious agent

7.2.6 Health Outcome of Interest (HOI)

Health Outcomes of Interest (HOIs) are pre-specified clinical events or outcomes that are collected according to the protocol. HOIs may be represented as diagnosis, treatment or procedures. Examples of HOIs include syncope or hypoglycaemia collected as study endpoints. HOIs must be assessed as part of AE collection and may meet criteria for AE reporting. Specifically, the investigator must assess each HOI for serious criteria and causality. If the HOI meets criteria specified in the protocol for AE reporting, then it must be reported as such.

7.2.7 Sponsor's product

Sponsor’s product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

7.2.8 Causality Assessment

A causality assessment is the determination of whether or not there is at least a reasonable possibility that a product caused the adverse event. Causality must be recorded on the AE form by the investigator for each reported event in relationship to a Sponsor's product.

Primary Data Collection

The assessment of causality is to be determined by an investigator who is a qualified healthcare professional according to his/her best clinical judgment. Use the following criteria as guidance (not all criteria must be present to be indicative of causality to a Sponsor's product): There is evidence of exposure to the Sponsor's product; the temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable; the AE is more likely explained by the Sponsor's product than by another cause.

A qualified healthcare provider (Dr. Korenblat and/or Dr. Li) will review the measures collected for any potential AEs. They will evaluate each SAE for causality and record causality on the AE form for each event reported.

8 Statistical Analysis Plan

8.1 Statistical Methods

Aim 2 Analytic Methods: For all analyses, descriptive statistics (e.g., frequencies, tendencies, variability) and diagnostic plots will be completed on all variables. Data will be examined for outliers and tested as appropriate for normality, linearity, and homoscedasticity. Appropriate corrective strategies, such as transformations, use of robust methods, or data reduction, will be used if problems are identified. These preliminary analyses are necessary to ensure high quality data and to test assumptions of the proposed models. We will also compare basic demographic and clinical characteristics between study enrollees and eligible refusers to characterize the representativeness of the included patients. We will also examine within group differences in our outcomes (knowledge, decisional conflict, decision self-efficacy) among patients pre- and post-use of the DA in a multivariable linear regression model controlling for up to 5 independent covariates (e.g. age, stage of fibrosis, health literacy). We intend to include knowledge, decisional conflict, and decision self-efficacy as primary outcomes in three separate multivariable models, age and stage of fibrosis as planned covariates in all models. Health literacy will be included as a covariate in the model with knowledge as an outcome. Others will be added if significant at the bivariate level. The knowledge scale that we develop will be pilot tested with patients as well. We will assess scale reliability using Cronbach's alpha.

8.1.1 Primary Objectives

For pilot testing of the tool in Aim 2, we will collect demographic information and measure decisional conflict, change in decision self-efficacy, change in knowledge about HCV treatment risks and benefits among patients with advanced CKD, DA usability, and the match between patients' intended choice and their stated preferences.

8.2 Bias

8.2.1 Methods to Minimize Bias

During the pilot phase (Aim 2), there is a chance of social desirability bias occurring. Social desirability bias is a type of response bias where participants give answers that are more favorable to the interviewer. We will reduce this bias by choosing the wording for our questions and materials carefully, using validated measures when available for Aim 2, assuring them there are no right or wrong answers, and reminding them that we are here to learn from them.

Confounding is often mentioned as a "mixing of effects" wherein the effects of the exposure under study on a given outcome are mixed in with the effects of an additional factor (or set of factors) resulting in a misrepresentation of the true relationship [61]. We controlled for cofounding during study planning, where we specified our inclusion criteria and will control at the time of analysis by computing a multi-variable regression analysis.

We also selected a repeated measures/within subject design to minimize potential bias of a randomized trial randomizing at the patient level, where clinicians could contaminate the control group if they learned communication techniques after using the DA and applied them to controls as well.

8.2.3 Limitations

- Aim 2 is a single site study with a moderate sample size, so results might not be generalizable. To address this, we plan to include a national sample of clinicians in Aim 3.
- Since there is no use of randomization in Aim 2, results should be interpreted as demonstrating preliminary efficacy of the tool. For example, we will not know if there were learning effects of taking the same measures twice or whether the DA led to changes in pre-post test outcomes. We will compare results to other studies of DAs and will design future larger studies with a control group for comparison.

8.3 Sample Size and Power Calculations

Sample size and power were calculated using Power Analysis and Sample Size Software (PASS 11) [53]. We conducted our sample size calculation based on our expected change in decisional conflict based on past studies using DAs overall [54], and by consulting with the scale's user manual [55]. We expect a 15 point reduction in decisional conflict scores pre- and post- use of the DA and an effect size of 0.35. To examine within group differences in decisional conflict among patients pre- and post-use of the DA, we will conduct a paired-samples t-test. A sample size of 70 patients allows us to achieve a power of 80%, using two-sided t-test with a type I error of 5%.

We will also examine within group differences in our outcomes among patients pre- and post-use of the DA in a multivariable linear regression model controlling for up to 5 independent covariates (e.g. age, health literacy, race/ethnicity, decision role preference, clinical characteristics).

9 ADMINISTRATIVE AND REGULATORY DETAILS

Because we have a fully executed contract that has been reviewed by legal teams from both Merck and Washington University, to the extent that any part of the protocol conflicts with the contract, the contract will control decisions.

9.1 Confidentiality

The research team understands that the protection of participants is of the utmost importance when conducting research with human subjects. In order to protect the rights and safety of participants, we will comply fully with the Code of Federal Regulations Title 45 Public Welfare, Department of Health and Human Services, National Institutes of Health, and Office for Protection from Research Risks, Part 46 Protection of Human Subjects. All aspects of the research projects (protocol, questionnaires, and recruitment materials) will be submitted to and reviewed by the Washington University institutional review board.

9.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the Institutional Review Board, Ethics Review Committee or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

Data and Safety Monitoring Plan: The PI and study team will be responsible for ongoing and continuous monitoring of human participants in the study, as guided by the Human Research Protection Office (HRPO) at the Washington University School of Medicine (WUSM). A data safety monitoring plan (DSMP) has been developed in conjunction with WUSM. This is a minimal risk study and we do not anticipate safety concerns. DSMP components for this project include: IRB approval from institution; standard continuing review via IRB; all members of research team will complete university IRB training; and human subjects concerns as a standard agenda item for project meetings. Any adverse events will be reported to HRPO following WUSM procedures (i.e., within 7 calendar days for events other than serious health events) and to the study sponsor in accordance with Section 7.0. There is no penalty for refusing to participate or complete components of the study. The research team will discuss the logistics, safety issues, and mechanics of the study on a bi-weekly basis.

9.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative) or Institutional Review Board/Independent Ethics Committee (IRB/IEC), may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

Protection against risks: Study materials, including qualitative interview guide and survey items and scales will be selected to reduce burden to participants. In order to protect confidentiality, all written information and questionnaires will be kept separately from identifiable information in a locked cabinet. Identification data will be stored in a separate locked cabinet linked with participants' confidential ID numbers. Data will be organized and analyzed base on participants' ID numbers. All electronic files will be saved on a computer network which requires authorization from the Systems Manger to view, and individual files will also be password protected. All members of the research will have completed HIPAA and CITI training and will handle data with complete confidentiality. The only identification that will appear on any data collection instruments with project participants will be a participant identification code. Data will be reported in summary format only, with no individual characteristics shared.

9.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number and e-mail address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter study, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

9.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/sub investigator's responsibility to comply with any such request.

The investigator/sub investigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/sub investigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/sub investigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

9.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Pharmacoepidemiology Practice; and all applicable local laws, rules and regulations relating to the conduct of the clinical study.

To the extent it is consistent with the contract, the investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Pharmacoepidemiology Practice, standards and applicable local laws, rules and regulations; and, for each subject participating in the study, provide all data, and, upon completion or termination of the study, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the study in accordance with their institution's records retention schedule which is compliant with all applicable regional and national laws and regulatory requirements. If an institution does not have a records retention schedule to manage its records long-term, the investigator must maintain all documentation and records relating to the conduct of the study for 5 years after final report or first publication of study results, whichever comes later, per GPP guidelines. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. All study documents shall be made available if required by relevant regulatory authorities. The investigator must consult with the Sponsor prior to discarding study and/or subject files.

The investigator will promptly inform the Sponsor of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that site's IRB/IEC.

For a single-center study, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the study report that summarizes the study results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the study in the study's final report. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of study methods, appropriate enrollment of subject cohort, timely achievement of study milestones). The Protocol CI must be a participating study investigator.

9.4 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

9.5 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

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12 Appendices

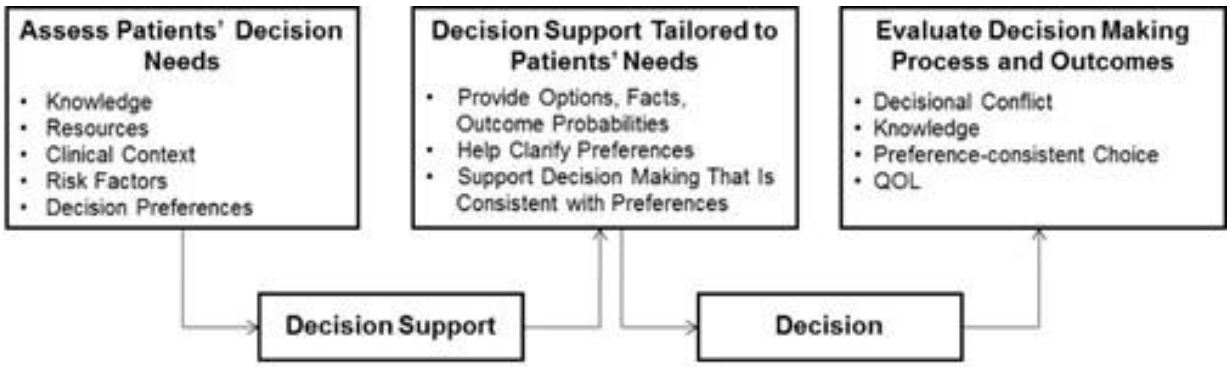

Figure 1. Decision Support Process Based on the Ottawa Decision Support Framework