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Patient Engagement and Study Design of PROP UP: A multi-site patient-centered prospective observational study of patients undergoing hepatitis C treatment

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Abstract

Background—New highly efficacious direct-acting antiviral (DAA) therapies are available to treat chronic hepatitis C viral (HCV) infection. Real-world, patient-centered data on harms and benefits associated with these therapies are needed.

Methods—PROP UP is a multi-center prospective observational study that plans to enroll 1,600 patients starting treatment with recently-approved DAA regimens. Informed by extensive input

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from a HCV patient engagement group who prioritized outcomes most important to them, patient-reported outcomes will be characterized using surveys at five time points: Baseline (T1), treatment week 4 (T2), end of treatment (T3), 12 weeks post-treatment (T4), 12 months post-treatment (T5).

Outcomes—(1) Changes in side effects, functioning, pre-existing conditions, and out-of-pocket costs during therapy (T1 vs T2/T3); (2) Medication adherence in relation to a history of mental health/substance abuse, treatment regimens, pill burden, reasons for missed doses, and cure rates; (3) Short term impact of cure on functioning and amelioration of symptoms (T1 vs T4); (4) Long-term treatment harms or benefits of cure on symptoms, side effects, pre-existing conditions, and functioning (T1 vs T5). Similarities between regimens will be examined where comparisons are appropriate and meaningful.

Conclusion—PROP UP complements previous clinical trials by focusing on patient-reported outcomes in a representative sample of patients treated in clinical practice, by collaborating with a patient engagement group, by characterizing the experiences of vulnerable subgroups, and by investigating long-term harms and benefits of treatments. PROP UP is designed to provide novel and detailed information to support informed decision-making for patients and providers contemplating HCV treatment (PCORI CER-1408-20660; NCT02601820).

Keywords

Liver; hepatitis; patient-reported outcomes; patient-centered outcomes research (PCOR); direct acting antiviral (DAA)

1.0 Introduction

Between 2.5 and 5.2 million people are estimated to be currently infected with chronic hepatitis C virus (HCV) in the U.S.[1-3], and 12,000 people per year die from liver-related complications such as liver failure, cirrhosis, and liver cancer[4,5]. People with chronic HCV often suffer from chronic, systemic symptoms, other chronic comorbidities, and poorer health-related quality of life (HRQOL), compared with the general U.S. population[6-9]. These individuals experience numerous physical and neuropsychiatric symptoms, such as fatigue, achiness, and depressive symptoms[8]. Comorbidities (e.g., psychiatric, addiction, diabetes, skin disorders, HIV) occur at higher rates compared to the general population[8-12]. HCV patients' poorer HRQOL remains significant after controlling for substance abuse[13,14]. The reasons for poorer HRQOL are multifactorial, but are likely related to symptoms resulting from years of chronic systemic viral inflammation in the central nervous system, comorbid conditions, social stigma, and anxiety related to deteriorating health[7,8,13,15-17]

Fortunately, the treatment for HCV has taken a quantum leap forward in the last 3 years with the approval of multiple direct acting antiviral (DAA) drug combinations by the Food and Drug Administration (FDA)[18]. Registration trials have consistently demonstrated that about 90% of treated patients achieve a sustained virological response (SVR, i.e., “viral cure”)[19-22], findings later replicated in real-world observational studies[23,24]. In addition to higher efficacy rates, the DAA regimens boast shorter durations and fewer side effects compared to previous regimens[22,23,25].

Given the rapid approval of DAAs in the last 3 years, minimal outcome data have been published. Data derived from registration trials are necessary but not sufficient. These trials often misrepresent the demographic distribution of the general HCV population, especially more vulnerable and traditionally 'difficult to treat' populations. Secondly, efficacy and adverse events have been the foci of these registration trials; however data derived from clinicians are known to under-report the frequency and severity of adverse events compared to patient-reported experiences[26]. Since most HCV symptoms and side effects are highly subjective (e.g. headaches, nausea), the correlation between clinician- and patient-reported side effects may be quite low[27]. Finally, the follow-up time during these trials has been too brief to capture longer-term data. Real-world observational studies have been conducted that generally replicate the findings from registration trials in diverse patients treated in clinical practice[23,24]. However, the outcomes were limited to efficacy and safety, and did not capture other important experiences that are also of concern to HCV patients.

Given these existing gaps in the scientific knowledge, patient-centered outcomes research (PCOR) studies in diverse and representative populations are needed to evaluate additional short-term and long-term harms and benefits that concern patients[28,29]. The Patient-Reported Outcomes Project of HCV-TARGET (PROP UP) is funded by the Patient Centered Outcomes Research Institute (PCORI) and is designed to characterize patient-driven outcomes before, during, and after regimens of DAA therapy (Clinical trial.gov: NCT02601820). PROP UP is a unique collaboration between clinical researchers, patients, and patient advocates. The objectives of this paper are to fully describe the PROP UP study protocol to lay the groundwork for future publications, and highlight the important role that patient engagement played during PROP UP development and execution.

2.0 Methods

2.1 Patient engagement during the development of PROP UP

Significant patient engagement during the development of a research proposal and execution of a study is a unique and defining feature of proposals funded by PCORI (www.pcori.org)[30]. Patient or stakeholder engagement refers to meaningful involvement of patients or other stakeholders throughout the research cycle, from design, to implementation, to dissemination[31]. Patient engagement is intended to lead to research studies being more patient-centric, relevant, useful, and transparent, and ultimately to a greater trust in and uptake of study results by patients, providers, and other stakeholders making treatment decisions. As such, patient engagement was an essential cornerstone on which the PROP UP study was built. Below, we describe how people affected by HCV directly informed the development, outcomes, and execution of the PROP UP study.

In the year before proposal submission, we conducted a formative content analysis of 45 patient interviews with patients being evaluated by clinicians for HCV treatment[32]. Participants were asked to free-list all potential types of information they felt were important to them for making an informed treatment decision or choosing between hypothetical treatment options. Nearly 100 different raw responses were elicited and coded into six broad categories that included 17 sub-categories in total. Nine of the 17 subcategories were informational categories that represented on-treatment or post-treatment harms or benefits

and for which the empirical literature appeared lacking to fully address patients' informational needs. The other subcategories included static information that was readily obtainable from the current literature or online sources (e.g., “What is HCV?”, “How is HCV transmitted?”) and thus did not require additional investigation. Therefore, the nine informational topics that warranted additional investigation represented plausible study outcomes to be evaluated in PROP UP.

Meanwhile, in May 2013, about 9 months prior to submitting the initial PCORI proposal, we established a HCV Patient Engagement Group (HCV-PEG) at the University of North Carolina (UNC) to serve as our patient research partners throughout the project. The UNC HCV-PEG included a diverse group of seven people, ages 41 to 65, who were infected with HCV, three previously treated and cured, three were undergoing treatment, and one was contemplating treatment. One member is the founder and director of a national HCV patient advocacy organization (www.HCVadvocate.org). The HCV-PEG participated in five, 2.5 hour meetings prior to the initial proposal submission to provide input on many proposed study features described in detail below.

The first task of the HCV-PEG was to prioritize the nine informational subcategories derived from the 45 qualitative interviews. Table 1 provides the prioritized rankings by the HCV-PEG of the nine subcategories that reflected patients' informational needs. Several of these informational subcategories could translate directly into key patient-centered outcomes that we could evaluate in PROP UP. Once these patient priorities were elucidated, the investigators determined which outcomes were most feasible to capture given the study duration and resources.

Subsequent meetings with the HCV-PEG during study development addressed many other critical study elements, as detailed below. Most importantly, the HCV-PEG assisted the investigators in selecting the instruments that best captured several patient-centered outcomes. During one meeting, the members were presented with multiple instruments that could measure HRQOL, and after group discussion, the HCV-PEG recommended the instrument that they felt best captured their personal experiences. The study design elements for which the HCV-PEG provided relevant input included: (a) the informed consent process; (b) selection of survey assessment schedule; (c) survey data collection options; (d) subject reimbursement amounts; (e) retention strategies; and (f) weighing respondent burden against the value of knowledge to be gained by the instruments administered.

Meanwhile, a recent comparative effectiveness review from the Agency for Health Research and Quality (AHRQ)[33] and a subsequent AHRQ Future Research Needs[28] paper had identified additional gaps in the HCV literature with future research recommendations which were discussed with the HCV-PEG and considered during the development of PROP UP. Based on the identified gaps, AHRQ recommended that future studies enroll a broader spectrum of patients, including those with medical and psychological comorbidities, and studies to understand the real-world effects of treatments, including those related to treatment adherence. Other identified gaps led AHRQ to also recommend studies to assess important long-term clinical benefits of treatment, such as the effect of viral cure on long-

term HRQOL, potential long-term treatment harms, and importantly, studies not funded by pharmaceutical companies.

A final consideration during refinement of the study were recommendations that resulted from a PCORI-sponsored workshop on HCV with attendees including researchers, patients, advocates and other stakeholders[29]. The recommendations for future PCOR studies included a) evaluation of therapies to demonstrate which are associated with the best outcomes and fewest side effects; b) long-term toxicities of the HCV regimens; c) whether traditionally 'difficult to treat' subgroups have different outcomes; d) how various treatments compare regarding medication adherence; and e) whether treatment ameliorates the common diverse symptoms associated with HCV.

At the time of our second proposal submission in January 2015, no study had yet addressed the research needs posed ubiquitously by patients, stakeholders, and funding agencies. Therefore, PROP UP was designed to address several of these evidence gaps. The research protocol described below represent the current protocol which was modified in June 2016 to keep pace with the rapidly evolving HCV treatment landscape and include the most recently-approved DAA therapies. Below we describe the study protocol, including key study features influenced by HCV-PEG feedback.

2.2 Study Design

Brief summary: PROP UP is a multi-center, prospective, observational, patient-centered outcomes research study that plans to enroll 1,600 patients across the U.S. to characterize short-term and long-term harms and benefits associated with HCV treatment. Patients being prescribed any one of the five DAA regimens with or without ribavirin (RBV), listed in Table 2, are eligible to participate. Data are collected directly from study participants to capture patients' experiences before treatment (T1), early in treatment (T2), late in treatment (T3), 12 weeks post-treatment (T4), and one year after HCV treatment ends (T5). At each time point, participants respond to several patient-reported outcome (PRO) instruments to measure common HCV symptoms, comorbid medical conditions, treatment side effects, HRQOL, out of pocket (OOP) costs and medication adherence. No drug therapy is administered for research purposes. Clinical providers at each site are responsible for selection of treatment regimens, initiation of treatment, monitoring the patients, and for providing standard of care practices, which may include drawing blood, performing laboratory tests, biological monitoring, or conducting physical exams. The clinical and laboratory data are extracted from medical records at baseline (T1) and 12 weeks post-treatment (T4). This study is entirely observational in nature and designed to characterize patient experiences in representative "real world" clinical settings. Duration of patient's participation may range from 14 to 21 months, depending on how quickly they begin treatment and the length of the prescribed regimen (8 to 24 weeks).

2.3 Specific Aims

Aim 1: Evaluate changes from baseline (T1) to during treatment (T2, T3) to characterize harms associated with each treatment regimen in terms of the following measures:

1a. The Memorial Symptom Assessment Scale (MSAS)[34,35];

1b. Side effects as measured by multiple Patient-Reported Outcomes Measurement Information System® (PROMIS®) measures[36] and the Headache Impact Test (HIT) measure[37];

1c. HCV-specific functional status as measured by the HCV-PRO[38,39];

1d. Pre-existing medical conditions; and

1e. Cumulative out of pocket (OOP) costs during treatment.

Aim 2: Evaluate medication adherence, with an emphasis on comparing patients with and without history of mental health/substance abuse:

2a. Characterize and compare the two groups on medication adherence while accounting for treatment regimen and pill burden;

2b. Estimate the effects of pill burden on medication adherence;

2c. Estimate the prevalence rates of reasons for nonadherence;

2d. Estimate the effect of medication adherence on SVR at 3 months post-treatment.

Aim 3: Evaluate changes from baseline (T1) to 3 months after end of treatment (T4) to characterize short-term benefits of cure in the combined sample of patients:

3a: Amelioration of HCV-associated symptoms as measured by the MSAS and PROMIS® instruments; and

3b. HCV-functional status as measured by the HCV-PRO.

Aim 4: Evaluate changes from baseline (T1) to 1 Year (T5) after end of treatment to characterize long-term benefits of cure or harms of treatment:

4a. Long-term symptoms as measured by the MSAS;

4b. Long-term side effects as measured by PROMIS® instruments;

4c. Pre-existing medical conditions;

4d. HCV-functional status, as measured by the HCV-PRO; and

4e. Differences in 4a-4d between patients with and without cirrhosis.

Auxiliary Aims: The primary objective of PROP UP is to characterize a broad spectrum of benefits and harms associated with DAA treatment and viral cure as outlined in the specific aims. However, we will also take the opportunity to examine similarities and differences in these outcomes between the treatment regimens using causal inference methods where comparisons are deemed meaningful.

2.4 Study Methods

2.4.1 Target Population and Sample Size—To enroll 1,600 patients, it is estimated that approximately 1,920 patients will need to be recruited and consented. Based on clinical

experience at our subsites, we anticipate a 15% -20% enrollment failure rate due to insurance payers denying treatment approval. Numerous private and public insurance payers in the U.S. are currently limiting treatment coverage to patients with advanced fibrosis or cirrhosis (stage 3-4), and despite scientific justification, are denying coverage to patients with certain characteristics[40,41], although this trend appears to be slowly decreasing with more payers loosening restriction policies. As a result of these insurance issues, we estimate that 1,600 out of 1,920 patients who have given consent to participate will eventually be enrolled and will meet the following enrollment criteria: (1) written consent, (2) completion of baseline PRO surveys, (3) administer one dose of medication within 90 days of baseline PRO assessment.

2.4.1.1 Inclusion Criteria: Under the current protocol approved in June 2016, eligible patients include those diagnosed with chronic hepatitis C, any HCV genotype 1-6, who are English-speaking, age 21 years or older, and have been medically cleared for treatment by a hepatology clinician and prescribed one of the five DAA regimens listed in Table 2. The first version of the protocol spanning December 2015 through May 2016 included only patients with HCV genotype 1 being prescribed one of the first two regimens listed in Table 2.

2.4.1.2. Exclusion Criteria: Patients who are unable to provide written informed consent, currently participating in a pharmaceutical-sponsored drug trial of HCV treatment, have major cognitive or mental impairment; are unable to read or speak English; or are unwilling or unable to complete surveys, will be ineligible for the study. Currently in clinical practice pregnant and breastfeeding women are not being treated with antiviral medications due to potential teratogenicity, and therefore are not included in the study population.

2.4.1.3. Study Discontinuation: Participants who start treatment without completing baseline pre-treatment PROs are considered enrollment failures and not followed longitudinally. Once participants complete baseline surveys and commence therapy, they are officially enrolled. We do not anticipate many reasons to withdraw participants after treatment begins because of the short duration of treatment. In keeping with the goal of assessing patient outcomes in “real world treatment settings,” if a patient commences but prematurely discontinues therapy, he/she will be encouraged to continue in the study and complete the remaining assessments. Participants will be discontinued from the study at any time if they withdraw informed consent verbally or in writing.

2.4.2 DAA Regimens—The names and characteristics of the five DAA regimens being evaluated are listed in Table 2. Each of these regimens may also be augmented with daily ribavirin (RBV), which adds to pill burden (additional 5-6 pills per day) and side effect profile. All regimens are associated with cure rates of 90% or greater in Phase III registration trials and observational studies, with the exception of patients with cirrhosis who typically have lower cure rates. The majority of patients undergo treatment for 12 weeks, while some are approved for 8 weeks, and patients with cirrhosis may be approved for 24 weeks. Previous trial and registry data focus mainly on SVR and clinician-assessed adverse events. Trials of sofosbuvir have included PROs to evaluate HRQOL, fatigue and work productivity[42,43]. These studies have shortcomings, including potentially limited

generalizability to patients treated outside of registration trials[44]. Currently, no information exists to evaluate patient-reported similarities or differences among these regimens.

2.4.3 Clinical Settings—Table 3 lists the 11 centers in the U.S. currently collaborating on PROP UP, most of which were participating sites in the parent HCV-TARGET clinical registry and network[46]. The first nine sites represent liver clinics associated with large academic medical centers. The last two sites were added in September 2016 to bolster enrollment, and represent community-based private practice gastroenterology centers. Each site has a designated primary investigator. All sites are under the jurisdiction of their local Institutional Review Board (IRB) and obtained approval prior to study initiation. The two new private practices report to the UNC IRB.

2.4.4 Data Coordinating Center—The Data Coordinating Center (DCC) and Centralized Call Center (CCC) reside at UNC. The DCC is responsible for overseeing data collection through frequent monitoring and querying of the data for weekly reporting. The DCC meets weekly to discuss recruitment and other data collection topics. The CCC is responsible for the completion of all follow-up phone surveys for all subsites. The CCC monitors and tracks participants' progress through all follow-up study time points and administer phone surveys within pre-established assessment windows.

2.4.5 Recruitment, Consent, Enrollment—See Figure 1 for study flowchart. Patients who meet inclusion criteria and have been written a prescription for one of the five DAA regimens are invited to participate and screened. Patients are recruited and consented in-person in the clinic. Research coordinators also recruit and consent by phone, after a recruitment letter and consent forms are mailed. The HCV-PEG recommended that patients be consented in-person in the clinic to establish rapport and explain the study most clearly; however, we found that obtaining consent via phone was necessary to contact patients who cannot be recruited in clinic due to constrained time and resources. Each site maintains its own secure de-identified screening log to capture information on number of refusals, refusal reasons, age, sex, and race, necessary to examine basic sampling bias and generalizability concerns. At time of consent, research coordinators provide patients with instructions for an OOP Cost Log and envelope for receipts as tools to help participants track treatment-related costs. These tools were recommended by the HCV-PEG to help participants track treatment expenses. Participants are asked to refer to these tools when responding to questions related to OOP costs associated with HCV treatment. When a consented participant has initiated DAA therapy, the site coordinator officially enrolls the participant in the longitudinal study. Baseline PRO measures need to be completed within 90 days prior to starting treatment. Site coordinators confirm enrollment criteria and enter treatment start date, prescribed regimen and treatment duration. These data trigger the scheduling of all subsequent surveys.

2.4.6 Data Collection

2.4.6.1 Web-based data capture: All data collected for PROP UP are directly entered and stored in the web-based research electronic data capture system, called *REDCap* (https://projectredcap.org/). The REDCap system is a secure, web-based application designed to support distributed data collection in biomedical research studies. The REDCap database is

stored, maintained, and monitored by the DCC. At each clinical site, authorized research coordinators have REDCap access to enter and edit data only for the participants at their site. REDCap automatically maintains an audit trail of all users and all activity. The database is incrementally archived. The REDCap application is hosted on a secure server environment located at UNC.

2.4.6.2 Data collection schedule: The data collection schedule for PROs (five time points) and clinical laboratory data (two time points) is displayed in Table 4.

2.4.7 PRO Data Collection—Baseline PRO data need to be collected within a 90 day window *prior* to the participant taking their first dose of medication. Ninety days provides sites with adequate time to obtain insurance approval for the prescription, which can often encounter delays.

The HCV-PEG recommended giving participants three options by which to complete PRO survey assessments: in clinic with a research coordinator; over the phone; or directly entered into the REDCap system by the participant. Follow-up PRO surveys can be completed over the phone with the UNC CCC or directly by the participant into REDCap.

2.4.7.1 PROs collected in clinic: Study participants who are recruited during a clinic visit by a research coordinator may respond to PRO surveys on a study laptop with assistance from the coordinator. Participants' responses to all PRO items are kept confidential by research coordinators and not shared with any of the patients' clinical providers. Site research coordinators who consent and collect data are independent of clinical staff at all sites, with the exception of one site where a mid-level provider consents participants but a coordinator collects the patient data.

2.4.7.2 PRO collected via home-based technology: At time of consent, patients may opt to provide an approved email address (stored in REDCap) and receive the PRO surveys via a link in an email. Patients with easy access to personal web-access technology (i.e., laptops, desktops, tablets, smart phones) may find this method more convenient and appealing. Our REDCap database is programmed to send emails containing a web-link based on the PRO assessment schedule. The web-link is unique to each subject at each assessment period.

2.4.7.3 PROs collected via phone: Participants can opt to complete PRO surveys via phone at baseline with the site research coordinator or with staff from the UNC CCC. Study staff contact participants at pre-approved phone numbers during each PRO assessment window and record participant responses into REDCap. The HCV-PEG indicated that phone surveys are a necessary option for many patients without access to technology or with low literacy levels.

2.4.7.4 Participant reimbursement: Given respondent burden, the HCV-PEG recommended the following reimbursement schedule for completion of each of the five PRO assessments: $25 each for T1, T2, and T3 surveys; $40 each for T4 and T5 surveys. The HCV-PEG recommended that these reimbursement rates are appropriate for completion of surveys that take 20-35 minutes to administer. They also encouraged increasing

reimbursement from $25 to $40 during post-treatment data collection to improve retention. Participants will not be dropped from the study for missing data collection at a single time point. We plan to capture data at all subsequent time points unless the patient is officially withdrawn from the study.

2.5 Measures

2.5.1 Overview—The survey instruments listed below are intended to capture several of the patient-centered outcomes listed in Table 1. These instruments were selected after several meetings and significant input from the HCV-PEG who reviewed instruments evaluating each construct, recommended the measures that best captured their experiences with HCV or HCV treatment, and where needed, helped to develop additional questions to ensure patient comprehension and usability.

2.5.2 Sociodemographic Survey—Sociodemographic questions are queried at T1 baseline to characterize the study sample and explore as potential confounding variables: age, sex at birth, race, marital status, educational status, income level, living situation, employment status, and health insurance status.

2.5.3 Memorial Symptom Assessment Scale (MSAS)—The MSAS is a reliable and validated instrument that will be used to measure a comprehensive set of pre-existing HCV-associated symptoms and potential treatment side effects[34,35]. The MSAS evaluates 32 prevalent disease symptoms or side effects common to medical treatments, enabling comparisons across various diseases and treatments. Respondents indicate the presence or absence of each symptom/side effect (Yes/No), and if present, rate the construct on severity, frequency and interference with functioning. An overall score and subscale scores are calculated. Higher scores indicate worse symptoms/side effects.

2.5.4 PROMIS® short forms—While the MSAS captures a comprehensive set of many potential HCV symptoms and treatment side effects, the PROMIS® short forms are used to measure very precise constructs most common or salient to HCV and its treatment. The PROMIS® short forms are a comprehensive set of reliable and validated instruments used across a wide range of medical conditions (https://www.assessmentcenter.net/). Importantly, these constructs are not confounded by items measuring other symptoms or aspects of HRQOL. Each PROMIS® short form includes a subset of 4-8 items from a larger item bank that were the best performing items in terms of content validity and reliability[47,48]. PROMIS® raw total scores are rescaled to a standardized T-score, which has a mean of 50 and standard deviation of 10 in the U.S. general population. Higher scores indicate worse symptoms/side effects. The following symptoms common to HCV will be measured: general cognitive concerns; pain interference; belly/liver pain; and depression. The following six experiences will be assessed as potential symptoms or treatment side effects: fatigue; sleep disturbance; nausea/vomiting; diarrhea; anger; and anxiety.

2.5.5 Headache Impact Test (HIT)—We measure headache, a commonly reported adverse event in DAA regimen trials, as a side effect of treatment with the validated 6-item Headache Impact Test[37]. Participants select responses from a 5-point Likert scale ranging

from “Never” to “Always.” Higher scores are indicative of worse headaches and greater impairment.

2.5.6 HCV-PRO—The HCV-PRO is a newly developed HCV-specific survey designed specifically to assess the well-being and functional status of HCV patients[38,39]. It was developed in accordance with the PRO guidelines issued by the FDA and demonstrated good reliability, and convergent validity was moderately high ($r > 0.50$). The scale includes 16 items that measure physical, emotional and social functioning, productivity, intimacy, and perception of quality of life. Participants select responses from a 5-point Likert scale: 1=“all of the time” to 5=“none of the time”. A higher total score indicates higher functioning.

2.5.7. Out of Pocket Costs—The OOP cost for patients who undergo DAA treatment is currently unknown, may vary considerably by insurance status, and is an important informational need for patients' contemplating HCV treatment[49]. The medical cost literature describes the importance of measuring both direct and indirect costs related to treatment[50]. Participants will be asked to estimate the cost of five direct and five indirect costs associated with HCV treatment. Direct costs include: HCV medication co-pays, co-pays for prescriptions to manage side effects, over the counter remedies for side effects, doctor visit co-pays, and blood draw co-pays. Indirect costs include: patient's missed work/lost hourly wages, caregiver lost wages, childcare expenses, borrowing of money, gas and mileage to attend clinic visits.

2.5.8 Voils Medication Adherence Survey (VMAS)—Medication adherence and reasons for missed doses are listed by federal funding agencies as important outcomes, may vary between treatment regimens, treatment durations, and among patient subgroups[28,29]. The VMAS consists of 3 patient-reported items that evaluated the *extent* of adherence using a 5-point Likert scale from 1=None of the time to 5=All of the time[51,52]. The items ask the participants how often they have missed doses over the past 7 days, averaged into a single score shown to be reliable (alpha = 0.84). Based on previous research in Dr. Voils' lab, a dichotomous variable will be created to categorize patients as 100% (those who answer “none of the time” to all three items) or <100% adherent (all others). The VMAS also assesses *reasons* for non-adherence. Out of a list of 23 potential reasons, the HCV-PEG selected the following eight items to capture the most likely reasons that patients might miss taking their HCV medications: “I was out of my routine,” “I forgot,” “I did not have my meds with me,” “I was too late with my dose,” “I was asleep,” “there was no one to help me,” “I ran out of my medication,” and “I could not get answers to my questions about the medication.” The VMAS has undergone qualitative testing in HCV patients on therapy and is currently being validated in patients on DAA therapy.

2.5.9 Medical comorbidities—At baseline, participants respond to a list of 34 chronic medical conditions regarding whether they (a) never had the condition; (b) had it previously; or (c) have it currently. At follow-up, participants respond to questions only for the conditions they endorsed having at baseline, and whether these conditions have ‘stayed the same,’ ‘got worse,’ or ‘got better’.

2.5.10 Psychiatric and Substance Abuse History—Participants respond to five questions related to psychiatric history and five questions related to drug and alcohol use. Psychiatric questions include psychiatric diagnoses, medications, services, and hospitalizations. Addiction questions were adapted from validated surveys and include frequency and amount of alcohol consumption and use of nonprescription street drugs and misuse of prescription medication[53,54]. Response to these questions will assist in categorizing participants with and without mental health and substance use conditions.

2.6 Data Analysis Strategy and Methods

2.6.1 Planned Manuscripts—The analysis plans are particular to the four specific aims and corresponding manuscripts in Table 5. These manuscripts will focus on interpretation of point- and interval- estimates of the effects of interest.

2.6.2. Analysis plans registered in the master protocol document—To help ensure reproducible results, the *a priori* analysis plans specify detailed steps for the main analyses along with sensitivity analyses to assess the robustness of the results to reasonable perturbations of the *a priori* assumptions, choices, and methods used. The plans also specify 1) use of supportive analyses of subscale items to aid our understanding and interpretation of the major analysis results; 2) a role for outcome-dependent exploratory analyses for hypothesis generation / refinement; and 3) necessary descriptive graphical and tabular methods used to characterize the participants, visualize the data and examine relationships among variables.

2.6.3 PRO change from baseline as a function of subgroup and treatment regimen—Because patients with cirrhosis and other subgroups may have different experiences during and after treatment, estimation and inference characterizing the treatment regimens will be subgroup-specific for some of the aims. In contrast, primary analysis of the benefits of viral cure will be all-inclusive with or without regard to treatment regimen. The general model for change from baseline for each outcome variable (e.g., Total MSAS score (TMSAS)) will condition on covariates including treatment regimen, subgroup status (e.g., cirrhosis), age, sex, ribavirin use, the subgroup-by-regimen interaction, and the baseline PRO score (e.g., TMSAS). The models fitted will provide parameter estimates used to obtain point estimates and confidence intervals (CI) to characterize each treatment regimen and/or each subgroup. A limited number of statistical hypotheses will be tested. For binary PRO scales or subscales, a similar strategy will rely on logistic regression model methods.

2.6.4 Supportive longitudinal analysis—Auxiliary analyses and exploratory analyses using methods appropriate for longitudinal PRO data (such as generalized estimating equations methods and linear mixed-effects models) will be used 1) to support and aid interpretation of the aim-specific results, and 2) to generate new hypotheses. From one occasion to the next, summary-score decrements will represent amelioration or disappearance of symptoms while summary-score increments will represent worsening or onset of symptoms or side effects. The individual's longitudinal trajectories of the scores will represent that individual's experience in terms of HCV symptoms. Ideally, any increment in symptoms and side-effects during treatment (T1 to T3) will be completely reversed by post-

treatment decrements (T3 to T5). These trajectories will be summarized descriptively via point- and interval- estimates of occasion-specific mean levels of summary scores. Additional auxiliary analyses of the symptom-specific sub-scores will be used to investigate whether side effects that begin during treatment tend to resolve and to investigate the incidence of new symptoms or side effects that appear after treatment ends. Patterns observed in the individuals' experiences will be summarized in terms of the proportion of patients for whom all treatment-related side-effects disappeared by T5.

2.6.5. Strategy for analysis of subgroup heterogeneity of treatment effects (HTE)—We will take the opportunity to examine similarities and differences between the treatment regimens, when possible and meaningful, using causal inference methods. Model-based methods will provide point estimates, confidence intervals and hypothesis tests needed to characterize and compare treatment regimens within subgroups. For each outcome variable these auxiliary comparisons of regimens may include an equivalence test procedure as well as a superiority test procedure. For purposes of hypothesis generation, exploratory analyses of HTE for additional subgroups will be performed.

2.6.6. Aim 1 (MS #1): Characterize PRO changes during treatment (T1 to T2/T3) —For each PRO score (or sub-score), the primary analyses described in this section will rely on linear models for change from baseline (T1 to the larger of T2 and T3) with covariate adjustment for the baseline PRO score (or sub-score), age, sex, ribavirin use, subgroup, treatment regimen, and subgroup-by-regimen interaction.

Aim 1a. MSAS: As an aid to interpretation of the main results for the TMSAS score, and for hypothesis generation, the three MSAS sub-scores (frequency, severity, distress) and for the 32 individual symptoms / side effects will be explored; e.g., the incidence of new side effects and exacerbation of existing symptoms during treatment will be characterized.

Aim 1b and 1c. PROMIS, HIT and HCV-PRO: As an aid to interpretation of the main results for the 10 separate PROMIS T-scores and the HIT score, supportive tabulations for the individual survey items will be examined.

Aim 1d. Pre-existing medical conditions: For each of the conditions we will summarize the frequencies of changes in status during treatment (improves, stays the same, worsens). Further exploratory analyses will be used to generate new hypotheses.

Aim 1e. OOP Costs: Patient-reported cumulative direct costs and indirect costs during treatment will be examined on $\log_{10}$ scale. Generalized log-linear models will be used for purposes of sensitivity analyses. The co-variation of OOP costs with other outcomes (e.g., treatment adherence) will be explored in order to generate new hypotheses.

2.6.7. Aim 2 (MS #2): Characterize patient-reported medication adherence, with emphasis on patients with and without mental health/substance abuse histories—The analyses concerning medication adherence will be based on patient-reported VMAS scores collected at T2 and T3.

Aim 2a. Mental Health or Substance Abuse History: In terms of dichotomized VMAS scores, patients with and without a history of mental health or substance abuse problems (MH/SU Hx) will be characterized and compared. About 50% of participants will have a MH/SU Hx. About 75% of all participants are expected to report 'high' (100%) adherence. We hypothesize that the two subpopulations are equivalent in regard to the rate of perfect adherence ('equivalent' defined to mean the rate difference < 5%). A 5% difference was recommended by the HCV-PEG as suggesting a minimally clinically important difference. Individual adherence may vary depending on treatment regimen, pill burden and patient characteristics. The adherence literature suggests that adherence decreases as the number of pills or dosing times in the regimen increases[55]. The primary characterization of each subgroup, and their comparison, will rely on a logistic regression model conditional on subgroup, pill burden, cirrhosis status, age and sex. The rate of 'high' adherence for each subgroup, and the magnitude of difference between those two rates, are of greatest interest. An equivalence test procedure will be used to test the null hypothesis that the two rates are not equivalent. To generate new hypotheses, variations on the model will be explored using additional or alternative covariates such as OOP costs, educational status, income level, employment status, and health coverage, and selected two-way interactions thereof.

Aim 2b Pill burden: In a combined sample, we will investigate the relationship between adherence and pill burden via the logistic regression model for adherence conditional on pill burden and the following covariates: cirrhosis status, age and sex. The analysis will focus on point- and interval-estimates of the rate of perfect adherence as a function of pill burden evaluated at reference levels of the covariates.

Aim 2c. Reasons for missed doses: In a combined sample, descriptive methods will be used to investigate prevalence of eight common reasons patients missed taking their medication. Tabulations will be based on the responses of participants who reported imperfect adherence ($n \approx 400$).

Aim 2d. Sustained Virological Response: In a combined sample, about 1450 of the 1600 participants are expected to achieve SVR. The relationship between adherence captured at T2 and T3 and SVR rates captured at T4 (3 months post-treatment) will be explored using a logistic regression model for SVR conditional on the following covariates: cirrhosis status, age and sex. Variations on this model will be explored. The analysis will focus on point- and interval-estimates of the SVR rate as a function of adherence and pill burden evaluated at reference levels of the covariates.

2.6.8. Aim 3 (MS #3): Characterize PRO changes after end of treatment (T1 to T4)—For each PRO measure, we will report point- and interval- estimates of the mean change from T1 to T4 in patients who achieved cure (n~1450). In the same manner we will characterize the experience of those who did not achieve cure (n~150). These primary analyses will rely on a linear model for change from baseline for each PRO variable conditional on covariates which include the baseline PRO score, cirrhosis status, age and sex. Secondly, we will use multivariable regression analyses to investigate factors and interactions which may be predictive of mean change in PROs in the patients who achieved

cure. The exploratory analyses will also include investigation of differences between those who did and did not achieve cure, Sensitivity analyses will include variations such as regimen-specific estimation of differences and associations.

Aim 3, MSAS, PROMIS, HIT and HCV-PRO: The measure-specific details of the analysis strategy will be similar to those described above for Aims 1a, 1b, 1c, and 1d.

2.6.9. Aim 4 (MS #4): Characterize PRO changes 1 Year after treatment ends (T1 to T5)—In order to evaluate benefits of viral cure, we will report change in mean PRO scores from T1 to T5 on all PROs in patients who achieve cure (n~1450) as well as in those who do not achieve cure (n~150). Secondly, we will conduct multivariable regression analyses to investigate factors and interactions that may be predictive of mean change in PROs in the patients who achieved SVR. These primary analyses will rely on a linear model for change from baseline for each PRO variable conditional on covariates which include the baseline PRO score, cirrhosis status, age and sex. The analysis will focus on point estimates and confidence intervals. In order to evaluate potential harms of treatment, we will evaluate the different regimens separately, and evaluate PRO changes suggestive of long-term treatment harms, adjusting for covariates such as ribavirin use, cirrhosis status, age, and sex.

Aim 4a, 4b, 4d, MSAS, PROMIS, HIT and HCV-PRO: The measure-specific details of the analysis strategy will be similar to those described above for Aims 1a, 1b, 1c, and 1d.

Aim 4c. Pre-existing medical conditions: For each of several patient-selected pre-existing conditions at baseline, we will estimate the proportion of patients who report that this condition stayed the same, became worse, or got better one year after treatment ends (T1 to T5).

Aim 4e. Cirrhosis effects: For each treatment regimen we will examine the influence of cirrhosis on change from baseline (T1 to T5) for each PRO score. The point- and interval-estimates of interest will be obtained from the models fitted for Aims 4a, 4b, 4c and 4d.

2.6.10. Auxiliary analyses comparing treatment regimens—The auxiliary analyses comparing regimens will require application of causal inference methods for models similar to those for Aims 3a, 3b, 3c and 3d.

Two stages of analysis: The causal inference analysis strategy comprises (1) a design stage involving estimation and use of a propensity score model for purposes of achieving balance of baseline covariates; and (2) an outcomes analysis stage for treatment effect estimation and inference separately for each outcome variable. For these two stages we may rely on the approach proposed by Cao et al.[56] building on previous work by Tan[57,58], Robins et al[59], Funk et al[60] and others. Rotnitzky et al[61] proposed a competing approach and compared the performance of their method to that of Cao et al.[56]. In the manner of Cao et al., we may use an improved doubly robust estimator obtained via enhancements in the estimation of the propensity score model and the inverse-probability weighted outcome model. Confidence

intervals will rely on bootstrap methods. Similar analytic methods will be employed to compare patient subgroups or different treatment durations.

Sensitivity analyses and diagnostics: Both stages will involve careful use of diagnostic methods (e.g., for covariate balance) and an extensive set of sensitivity analyses. Additionally, to ensure covariate balance in each of the two cirrhosis subgroups, it will be necessary to take steps in the design stage to, for example, appropriately account for subgroup differences in the propensity score model and examine subgroup-specific diagnostics for covariate balance and for propensity score distribution overlap.

Unverifiable assumptions: Useful assumptions, such as "no unmeasured confounders," are unverifiable. Although limited by the necessity of making additional assumptions and conjectures, efforts will be made to investigate the potential magnitude of residual bias that would exist if, for example, any unmeasured confounders exist.

2.6.11. Methods for Coping with Missing Data—The analysis plan relies on an extensive set of covariates measured at baseline. For purposes of estimation of propensity score models in the design stage, missing covariate values will be addressed via multiple imputation; furthermore, for each participant, the resulting multiplicity of propensity scores will be averaged together as proposed by Mitra and Reiter[62]. The alternatives (e.g., average results from multiple outcome models) will be explored for purposes of sensitivity analysis. More generally, best practices for dealing appropriately with incomplete data, especially PROs, will depend on the documented causes of the missing, censored, or coarsened values. Every effort will be made to document the causes and to avoid incomplete data by capturing the PRO data. Depending on the mechanisms which cause loss-to-follow-up for outcomes such as the MSAS at 1 year, multiple imputation methods may be appropriate. Competing model-based methods will be examined for purposes of sensitivity analysis.

2.6.12. Sample Size Considerations—The target sample size for enrollment in the PROP Up Study is 1,600 participants. The final sample size will depend on rates of recruitment, attrition, costs and funding constraints. The rationale for this choice of target sample size was based on aim-specific considerations of the availability of eligible subjects, anticipated rates of recruitment, funding and the length of time available to conduct the study, the per-subject costs in time and effort, considerations of the anticipated levels of precision of estimators, and considerations of the anticipated levels of power of a small number of statistical hypothesis tests. Participants receiving Harvoni® are expected to comprise about 60% (n~960) of the participants, those on Viekira Pak® will comprise about 5% (n ≈ 80), those on Zepatier® about 10% (n ≈ 160), those on Epclusa® about 20% (n≈320), and those on daclatasvir/sofosbuvir about 5% (n≈80). Due to the rapidly changing treatment options and decisions made in real world clinical practice, the number of patients on each treatment regimen will be uneven and unpredictable. In each treatment cohort, subgroups of interest are expected to be about equally prevalent; for example, about 50% will have cirrhosis, and about 50% are expected to have a history of mental health conditions or substance abuse. In contrast, stratification by SVR will yield subgroups of unequal size,

as 90% of the participants in each treatment regimen are expected to achieve similar SVR rates across all treatment regimens.

3.0 Discussion

PROP UP is a 3 year PCORI-funded multi-site prospective observational study of up to 1,600 patients with chronic hepatitis C undergoing treatment in the U.S. with one of five new DAA treatments. PROP UP will provide an in-depth characterization of patients' experiences with these DAA treatments utilizing PRO surveys to evaluate HCV symptoms, treatment side effects, medication adherence, out of pocket costs, long-term harms, and long-term benefits of viral cure. In line with PCORI's mission, patient engagement was central to the development of PROP UP[63-65]. Study outcomes and measures were chosen by patients affected by the disease who were heavily engaged as research partners to ensure that the findings are relevant and useful to the HCV community. Data collected for PROP UP will allow the investigative team to answer several critical questions posed by patients, providers and other stakeholders with the intent of improving consumer knowledge and decision-making related to HCV treatment. The study will result in a better understanding of the prevalence of symptoms associated with HCV, patient-reported side effects associated with the new DAA therapies, medication adherence in patients with and without mental health and addiction issues, long-term harms of therapy, and potentially novel long-term benefits of viral cure. These findings will be disseminated with assistance from our HCV-PEG members, patient advocacy organizations (www.HCVadvocate.org), the PROP UP study website (www.med.unc.edu/PROPUP), and traditional scholarly venues to help patients, clinicians, and other stakeholders make more educated decisions about HCV treatment.

We have completed the first 1.5 years of PROP UP which has been devoted to study start-up and one year of recruitment. As of March 2017, our collaborating sites have collectively consented 1,552 patients, collected baseline data on 1,362, and enrolled 1,102 patients who have started DAA therapy. Enrollment failures have occurred with over 300 patients, approximately two-thirds due to insurance denials and one-third due to treatment starts in the absence of baseline PROs. Very few participants have been withdrawn from the study after enrollment and initiation of treatment. Data are being collected at T2, T3, and T4, with an admirable retention/completion rate of 94-98%. Study participants currently enrolled are 56% male, 60% White, 33% Black, 54% have a high school diploma or equivalent, 75% have an annual household income under $40,000, and 51% have evidence of cirrhosis. Over the next year, 11 academic and community-based liver centers will collaborate closely on completing recruitment and data collection. Sites are working hard to complete recruitment in 2017 in order to complete data analysis and disseminate study findings in 2018-2019.

The ongoing commitment of six original members of the UNC HCV-PEG who have brought the patient's voice to PROP UP since 2013, is noteworthy. The HCV-PEG has continued to be instrumental during study launch in Year 1, meeting with investigators multiple times to provide ongoing patient input and feedback. The members contributed in numerous meaningful ways this first year, including: (a) providing input on the consent form; (b) finalizing and beta-testing the PRO surveys in REDCap; (c) attending the PROP UP Kick-

off meeting; (d) agreeing on a Memorandum of Understanding; (e) attending meetings and conference calls with PCORI, coordinators, site investigators; (f) assisting with study protocol modifications; (g) providing suggestions for ways to bolster recruitment and maintain high retention, and (h) contributing personal interviews to the PROP UP e-newsletter. The members have also taken time to complete training in ethical conduct in research involving human subjects and conflict of interest. Moving forward, we expect the HCV-PEG to continue to bring the patient's perspective to bear on data interpretation, reviewing requests for secondary data analyses, identifying mediums for dissemination, and reviewing dissemination materials for the public to ensure it is patient-friendly and useful. By engaging patients as partners from the inception, the goal is to improve the relevancy, usability, transparency and uptake of the scientific data for decision-making purposes[63,64].

A few limitations to the study and challenges to overcome are worth mentioning. PROP UP is not a randomized controlled trial. The number of patients observed on each regimen will be unpredictable and assuredly uneven, but nonetheless reflective of current real-world clinical practice. It is possible that the number of patients on some regimens will be too low to conduct meaningful comparisons; nonetheless preliminary characterization of novel PROs will generate unique information and new hypotheses. Patients need to be English-speaking in order to participate. Data derived from participants in this study may not represent the entire population of people infected in the community who are not engaged in care in hepatology centers. Nonetheless the study will be highly representative of patients currently being approved for and undergoing DAA therapy in the U.S. These data could be limited in the future if the treatment regimens or characteristics of patients treated for HCV substantially changes. We have encountered challenges with consenting and collecting PROs from patients who do not initiate therapy due to insurance restrictions, or conversely, those who obtain rapid approval and start treatment before completing baseline PROs. Both scenarios waste coordinator time and effort and we are working diligently to overcome these challenges. As with all patient-reported data, there is the possibility of response bias and social desirability, especially to items that query adherence, mental health and substance abuse issues.

Finally, it has been incredibly difficult to keep pace with the rapidly evolving treatment landscape to capture information that will remain relevant to patients and stakeholders in the future. We implemented one major protocol modification in June 2016 to include Zepatier® and Epclusa®, both of which are espoused to have durability and therefore relevance to stakeholders in the future.

To conclude, several new DAA treatments are now available to treat chronic HCV, but the data on specific patient experiences during and after DAA therapy are limited and do not address the breadth of patients' informational needs to help them feel informed about treatment decisions. In the future, patients, providers, and other stakeholders will have multiple treatment options from which to choose. Many patients want to participate actively in the shared decision-making process, or at the very least, want to be well-informed consumers and participants of their own healthcare[66]. In order to feel well-informed, make the best decisions, and adhere to treatment, patients need detailed and sufficient information about these DAA regimens. The goal of PROP UP is to evaluate and characterize treatment

outcomes that matter most to people contemplating HCV treatment so that they have a better understanding of the illness, treatment, and potential harms and benefits of treatment, and can take these findings into account while making decisions about HCV treatment. Findings from the PROP UP study are forthcoming in the next couple of years.

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Abbreviations

DAA	Direct-acting antiviral
HCV	hepatitis C virus
HrQOL	health-related quality of life
FDA	Food and Drug Administration
SVR	sustained virological response
PCOR	patient-centered outcomes research
PCORI	The Patient Centered Outcomes Research Institute
HCV-PEG	HCV Patient Engagement Group
UNC	The University of North Carolina
AHRQ	The Agency for Health Research and Quality
MSAS	Memorial Symptom Assessment Scale
PROMIS®	Patient-Reported Outcomes Measurement Information System®
HIT	Headache Impact Test
OOP	Out of pocket
RBV	ribavirin
VPK	Viekira Pak®
IRB	Institutional Review Board
DCC	Data Coordinating Center
CCC	Centralized Call Center
REDCap	Web-based research electronic data capture system
TX	Treatment
AST	Aspartate Aminotransferase test
ALT	Alanine aminotransferase test
INR	International Normalized Ratio
MS	Manuscripts
TMSAS	Total MSAS score
CI	confidence intervals

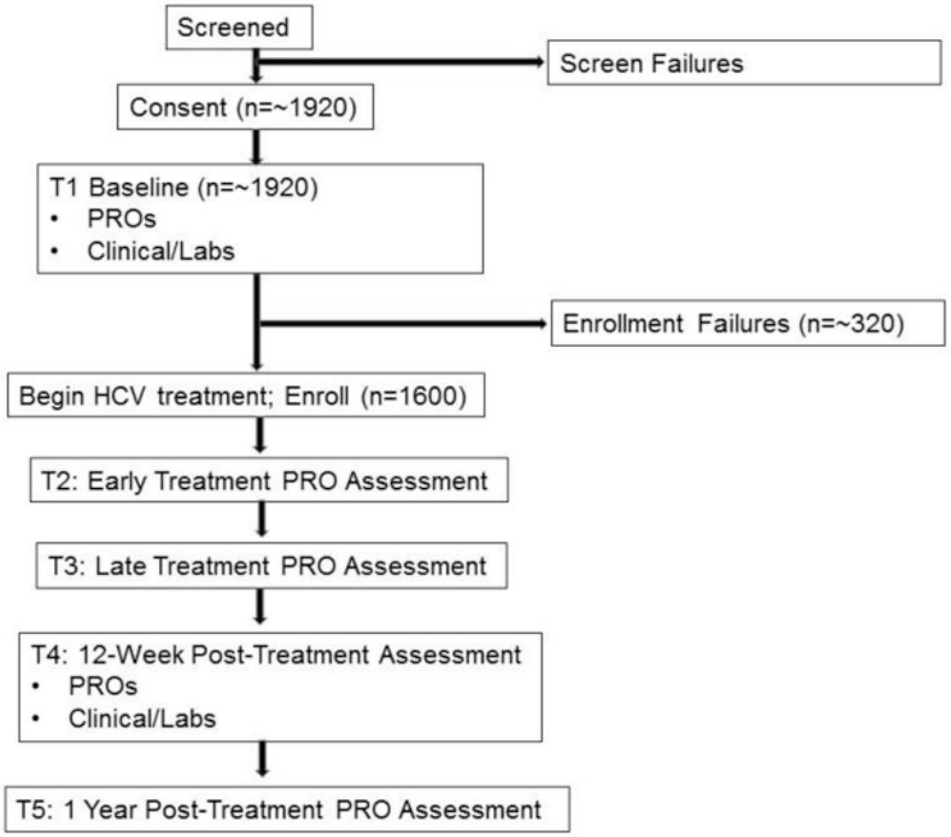

Figure 1. Study Flowchart

Table 1

Patients' informational needs translate into patient-centered study outcomes

Nine informational subcategories reflecting patients' informational needs	Patient-Centered Study Outcomes
“What are my chances of being cured?”	1. Cure rates
“What will treatment cost me?”	2. Out of Pocket Costs
“What are the side effects of treatment?”	3. Treatment Side Effects/Toxicities
“Will treatment hurt my liver?”	4. Harms to the Liver
“Will treatment worsens my ….(diabetes, depression, etc.)?”	5. Harms to pre-existing conditions
“Will I be able to function?” “What will my quality of life be like?”	6. Harms to functioning & HRQOL
“Will I live longer if I do treatment?”	7. Long-term survival
“Will my _____ improve with treatment?”	8. Benefits to pre-existing conditions
“Will I function better after treatment?” “Will I feel better after treatment?”	9. Benefit to functioning & HRQOL

Table 2

Characteristics of DAA Regimens

Brand Name	Generic Name	Genotype	Daily Pill Burden	Adverse Events**
Harvoni®	sofosbuvir/ledipasvir	1	1; 7 with RBV	Fatigue, headache, nausea[19]
Viekira Pak® *(VPK)*	ombitasvir/paritaprevir/ritonavir with dasabuvir	1	4; 10 with RBV	Fatigue, headache, nausea[20]
Zepatier®	elbasvir/grazoprevir	1	1; 7 with RBV	Headache, fatigue, nausea [22]
Epclusa®	sofosbuvir/velpatasvir	1 - 6*	1; 7 with RBV	fatigue, headache, nausea, insomnia, nasopharyngitis [21,25]
Daklinza®/Sovaldi®	daclatasvir/sofosbuvir	1 - 3	2; 8 with RBV	Fatigue, headache, nausea[45]

Note:

* Epclusa is the only pangenotypic drug that treats all genotypes.

** Adverse event data based on Phase III registration trial data.

Table 3

Collaborating Liver Centers

Institution	Location	Local Lead PI
Rush University	Chicago, IL	Nancy Reau, MD
Saint Louis University	St Louis, MO	Adrian Di Bisceglie, MD
University of Florida	Gainesville, FL	David Nelson, MD
University of Michigan	Ann Arbor, MI	Anna Lok, MD
University of North Carolina	Chapel Hill, NC	Donna Evon, PhD Michael Fried, MD Carol Golin, MD
University of Pennsylvania	Philadelphia, PA	Rajender Reddy, MD
Virginia Commonwealth University	Richmond, VA	Richard Sterling, MD
Yale University	New Haven, CT	Joseph Lim, MD
University of California at Davis	Davis, CA	Souvik Sarkar, MD, PhD
Asheville Gastroenterology Assoc.	Asheville, NC	William Harlan, MD
Wilmington Gastroenterology Assoc.	Wilmington, NC	William King, MD

Table 4

Data collection schedule

	T1	T2	T3	T4	T5
	Baseline Pre-TX[a]	**TX[a] Week 4**	**Late in TX[a]**	**12 weeks Post-TX[a]**	**1 year Post-TX[a]**
PRO instruments					
Sociodemographic	X				
MSAS Symptom Assessment	X	X	X	X	X
PROMIS Fatigue	X	X	X	X	X
PROMIS Pain Interference	X	X	X	X	X
PROMIS Sleep Disturbance	X	X	X	X	X
PROMIS Depression	X	X	X	X	X
PROMIS Cognition Concerns	X	X	X	X	X
PROMIS Irritability	X	X	X	X	X
PROMIS Anxiety	X	X	X	X	X
PROMIS Belly Pain	X	X	X	X	X
PROMIS Diarrhea	X	X	X	X	X
PROMIS Nausea/Vomiting	X	X	X	X	X
Headache Impact Test (HIT)	X	X	X	X	X
HCV-PRO	X	X	X	X	X
Medication Adherence		X	X		
Out of Pocket Cost		X	X	X	
Pre-existing conditions	X	X	X		X
PROMIS Stigma	X				X
Mental Health History	X				X
Alcohol and Drug History	X				X
Clinical and Lab Data					
Prescribed Treatment Regimen	X			X	
Prescribed Treatment Duration	X			X	
HCV Genotype	X				

	T1	T2	T3	T4	T5
	Baseline Pre-TX[a]	**TX[a] Week 4**	**Late in TX[a]**	**12 weeks Post-TX[a]**	**1 year Post-TX[a]**
HCV Viral Load	X			X	
Evidence of cirrhosis	X				
HIV status	X				
AST[b]	X			X	
ALT[c]	X			X	
Albumin	X			X	
Total Bilirubin	X			X	
Creatinine	X			X	
INR[d]	X			X	
Platelets	X			X	
Hemoglobin	X			X	
SVR				X	

Note: Valid PRO data collection windows are as follows: T1: Baseline PRO assessment within 90 days prior to start of treatment. T2: Treatment week 4 +/- 1 week (21-day window). T3: Late in treatment: during 7th-8th week of 8 week regimen (14-day window); during the 10th -12th week of 12 week regimen (21-day window); during the 22nd-24th week of 24 week regimen (21-day window). T4: 12 weeks after end of treatment +/- 3 weeks (49-day window). T5: 12 months after treatment ends +/- 2 months (84 day window).

[a] TX: Treatment

[b] AST: Aspartate aminotransferase test

[c] ALT: Alanine aminotransferase test

[d] INR: International normalized ratio

Table 5
Planned Manuscripts (MS) to Address Specific Aims

MS #1 PRO changes from baseline to during treatment (T1 to T2/T3). We will characterize each regimen in terms of treatment harms such as side effects. Auxiliary analyses will compare regimens.
MS #2 Medication adherence during treatment (T2 and T3). We will compare patients with and without history of mental health/substance abuse problems, characterize the effects of adherence on SVR rate, explore reasons for nonadherence, and evaluate effects of pill burden on adherence.
MS #3 Short-term PRO changes from baseline to 3 months post treatment (T1 to T4). We will characterize changes in patients who do and do not achieve SVR. Auxiliary analyses will explore differences between regimens.
MS #4 Long-term harms and benefits associated with HCV treatment (T1 to T5). We will evaluate changes in PROs one year after end of treatment. Auxiliary analyses will explore differences between regimens.