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PRIORITIZE

THE PRIORITIZE STUDY: A Pragmatic, Randomized Study of Oral Regimens for Hepatitis C: Transforming Decision-Making for Patients, Providers, and Stakeholders.

Version 5.0

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1. Protocol Version 5.0/Protocol Amendment/Rationale and Summary of Changes

The purpose of this amendment is to:

- Reduce overall sample size to at least 1700 participants consented to achieve at least 1228 participants who begin therapy.
- Remove interim safety analysis/stopping rule
- Remove VA consortium

1.1 Update in Sample Size

In summary, the update of the target sample size is entirely a consequence of the marked changes of cirrhotic participants being treated, restrictions related to Harvoni PA, and the discontinuation of regimen V. This amendment has been reviewed and approved by the Steering Committee. We believe that the changes are less than minimal risk and will increase the perceived benefit for study participants and other stakeholders. PRIORITIZE will answer critical questions regarding: 1) Rates of patients living with chronic hepatitis C who are being cured and durability of their cure, 2) side effects of the commonly prescribed drug regimens and other short and long-term treatment harms, and 3) patient-centered clinical benefits (changes in patient-reported HCV symptoms) and short/long-term liver disease progression or regression.

Since the initial design of this clinical trial in 2014, there have been dramatic shifts in the HCV treatment landscape in the US with respect to the type of patient who is presenting for treatment and the types of HCV direct acting antiviral (DAA) regimens available. Our original assumption that a high rate of cirrhotics would be treated was based on the available treatment data at the time. In 2013-2014, more than 50% of patients undergoing HCV treatment had evidence of cirrhosis. With rapid uptake of HCV treatment in this cirrhotic patient population, the prevalence of cirrhosis among untreated persons with HCV has decreased substantially to only 15 to 20%. This shift in the characteristics presenting for HCV treatment in the US is reflected in both the PRIORITIZE demographics to date (16% cirrhosis in over 1200 patients enrolled) and the HCV-TARGET observational registry (15% cirrhosis). Another dramatic shift in characteristics of patients presenting for HCV treatment is the increasing prevalence of Black Americans (42% of current enrollment) and persons who have never been treated (treatment-naïve 87% to date). Thus, compared to 2014, the typical patient presenting to health care providers for HCV treatment is more likely to be Black, have mild liver fibrosis, and have no prior HCV treatment. As such, the enrolled PRIORITIZE patient population differs from the initial expectations of the study team. This shift in patient demographics has affected our sample size.

From an enrollment metric standpoint, the study tracked behind projected milestones at a time in the study at which we had anticipated increasing enrollment. After extensive discussion with our site principal investigators and their study teams, the decreased pace of enrollment was attributed to the FDA approval of Mavyret™ (AbbVie Glecaprevir/Pibrentasvir or G/P). G/P was approved on August 4, 2017 for the treatment of persons with chronic HCV infection including all patients who are eligible for the PRIORITIZE study. Importantly, the wholesale acquisition cost (WAC)

of this regimen is markedly less (1/3rd) than that of other HCV drug regimens like Harvoni®. Further, most patients who do not have cirrhosis (the majority of the US population presenting for treatment) are eligible to be treated with Mavyret™ for 8 weeks (WAC $26,400 per course). From the time Mavyret™ was approved many payors, particularly Medicaid plans, changed their drug formularies to make Mavyret™ the preferred regimen. In addition, Mavyret was anticipated to replace regimen V, which would be withdrawn from the US market.

Based on these considerations, the PRIORITIZE Steering Committee discontinued new patients from being randomized to regimen V and proposed to end active enrollment of new participants in the PRIORITIZE study once an estimated 1228 patients combined between the regimens studied were dosed.

1.2 Safety Analysis/Stopping Rule

The original intent of the interim safety analysis was to screen for any safety signals that might warrant discontinuation of assigning enrollees to one of the treatment regimens. The interim safety analysis was removed from the protocol because that original purpose was rendered obsolete when it became clear that, by meeting the recruitment targets and milestones, enrollment would be completed before the results of the interim safety analysis could become available. The other alternative, pausing recruitment to allow time for the interim safety analysis, would have prevented recruitment from reaching its desired target. Lastly, each of the drugs being tested is a FDA-approved drug regimen that is being used per label in indicated populations (during study design drug Z had not been approved and label indication had not been fully known).

1.3 VA Consortium

After extensive discussions and delays, the VA consortium elected not to participate.

1.4 Impact of Amendment on Design and Randomization

The shift in demographics and influence of market forces on enrollment has important implications for current study design. First, we were (in 2014) anticipating a cirrhosis cohort of 625 patients per arm, which is now unrealistic and not reflective of current and future treatment populations. Second, we will have a much greater % of Blacks and treatment naive in our cohort, which is advantageous since these were important subgroups pre-specified in our data analysis plan. Thus, although we will lose precision and power for inferences regarding the cirrhotic sub-population, we will maintain or gain precision and power for inferences about the sub-populations that are increasing in prevalence.

2. BACKGROUND and INTRODUCTION

HCV is a devastating disease that impacts millions of Americans and contributes to impaired quality of life, morbidity, and premature death. HCV is curable with antiviral therapy, but only a minority of patients have been diagnosed and, of those, only a fraction have been offered treatment due to the difficult side effects of interferon-containing regimens. In 2014, the first all-oral HCV regimens were approved, marking a dramatic shift in treatment efficacy and tolerability. As we enter a new era of well-tolerated

therapies with high cure rates, we have a unique opportunity to begin to eradicate this chronic infection. However, as these all-oral therapies are introduced into practice, significant gaps in current evidence and high cost of treatment are impacting treatment choices and access to these medications. To narrow the evidence gaps, we propose a randomized, pragmatic clinical trial to compare the effectiveness of all-oral therapies to better understand the real-world efficacy and outcomes that matter most to patients and stakeholders.

2.1 Extent of HCV

It is estimated between 2% and 3% of the global population is infected with HCV, corresponding to approximately 130 to 170 million individuals.[1,2,3,4] In the United States (US), 3 to 4 million people are estimated to be infected, but no US survey has included institutionalized, incarcerated, or homeless individuals – populations with a high rate of HCV infection. Table 1 shows estimated rates in these populations. The prevalence of HCV in the US also shows marked gender, racial, and socioeconomic disparities. The US Preventive Services Task Force now recommends that Americans born between 1945 and 1965 (baby boomer birth cohort) undergo one-time screening for HCV infection to help identify individuals unaware of their chronic infection.[6] Thus, it is estimated that a large number of chronically infected adults will be identified in the next few years. Coupled with the advent of safer and more effective HCV treatments, this will lead to an influx of patients seeking anti-viral therapy, most of whom do not represent the "traditional" patients (healthy, Caucasian, male, minimal co-morbidities) studied in phase III clinical trials. For example, a high prevalence of HCV infection, 14%, is found in male non-Hispanic Black between the ages of 40-50, compared to 6% of male non-Hispanic whites in the same age group. The PRIORITIZE trial will enroll a more representative US population of HCV-infected people.

Table 1: HCV Prevalence Rates[5]	
US population	2%
Baby Boomer generation (born 1945-1965)	3.25%
Injection drug use > 10yrs	90%
Injection drug use < 10yrs	66%
Homeless persons	19 to 69%
Prisoners	29%
Individuals with mental illness	20%
Black American men (age 40-50 yrs)	14%

2.2 Impact of HCV and Cure

In the US, chronic HCV is the most common cause of liver disease and is responsible for at least 15,000 deaths annually and will continue to increase over the next few decades.[7,8] Despite what is thought to be a slow progression to cirrhosis, HCV-related mortality due to liver failure and liver cancer has increased substantially since 1995, especially in persons age 45 and older with the greatest increase in males and non-Hispanic blacks.[9] It has now become an important cause of premature mortality due to the relatively young age of those dying from HCV-related causes.[10] In addition to liver disease burden, chronic HCV impacts wellbeing and health-related quality of life with the most profound impairments in physical activity, energy, and vitality.[11] The main goal of HCV treatment is to eradicate HCV from the liver and blood thereby preventing progressive liver disease as well as the potential for transmission. Treatment effectiveness is measured by the sustained viral response rate (SVR), defined by the proportion of patients with undetectable HCV RNA in the blood 12 weeks after completing a course of treatment (SVR12).[12] SVR, analogous to cure of HCV infection, is associated with reduced risk of liver cancer, histologic

reversal of liver fibrosis, decreased comorbidities, and reduced risk of liver-related death.[13] A recent study of 21,000 U.S Veterans found that SVR was associated with a substantial decrease in all-cause mortality, even in those without evidence of cirrhosis suggesting an impact on non-liver related comorbidities (heart disease, diabetes, non-liver related cancers) presumably due to the impact of eliminating a chronic inflammatory disease.[14] In addition, SVR is associated with improvement in patient-reported quality of life (QOL) and fatigue, one of the most commonly reported systemic HCV-associated symptoms.[15] However, no data exist on improvements in other commonly reported systemic symptoms (e.g., sleep disturbance, achiness, irritability).[16] The improvement with SVR in morbidity, quality of life, fatigue and mortality presents a strong argument to provide treatment of all patients infected with HCV, regardless of degree of liver fibrosis. However, most of this data has been generated with interferon-containing regimens, and the lack of comparable data with direct-acting antivirals related to persistence of SVR, impact on patient-reported outcomes (PROs), and long-term treatment benefits and harms remain important gaps for all stakeholders that will be addressed in PRIORITIZE.

2.3 Gaps in Evidence

Important patient groups underrepresented in HCV clinical trials include Black Americans, older adults (> age 65), persons with active drug and alcohol use or mental illness, and patients with multiple co-morbidities. The generalizability of results to these populations is therefore unknown. In a recent phase III trial evaluating HARVONI® (ION-4)[17], the SVR for Black American participants was 10% lower than for other participants (89% vs. 99%) raising new concerns about this high-prevalence group. All phase III studies included patients ages 18-70 (very few above > 65) and, as such, the results may not be generalizable to older age groups. Also relevant is the exclusion from clinical trials of patients with histories of drug or alcohol abuse or mental health disturbances due to concern about safety and adherence to the protocol. Over half of patients infected with HCV suffer from drug and alcohol abuse and/or mental health disturbances.[18,19] Now that treatment regimens are interferon-free and better tolerated, these patients will be seeking treatment, yet the harms and benefits of these therapies for them remain completely unknown. Data regarding the effectiveness of new treatments in these and other patient groups is critical to inform the use of these regimens in clinical practice, particularly given the high financial cost of the regimens and the need to efficiently allocate resources. Important questions must be addressed to allow patients and clinicians to make the best treatment decisions: What is the SVR rate in a population of diverse patients and does SVR equal cure? What are the side effects for these regimens in sicker populations or those with comorbid psychiatric and substance use disorders? How do lower adherence rates impact SVR?

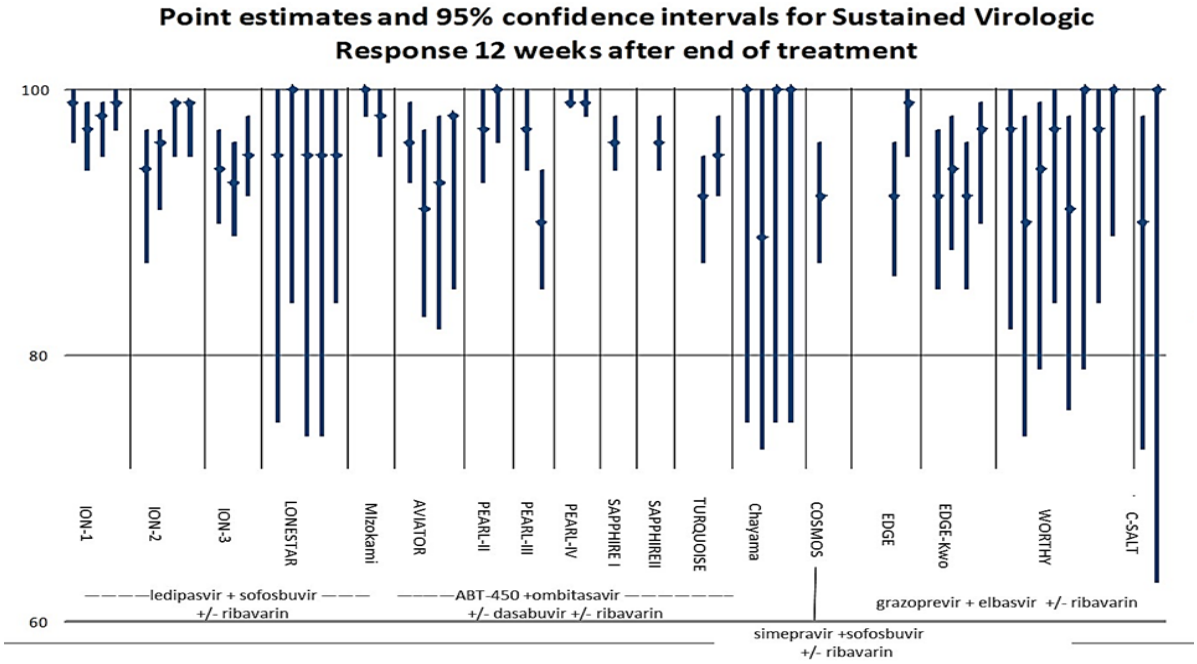
When the first two oral protease inhibitors (boceprevir and telaprevir) were introduced into clinical practice, the risk of severe adverse events approximately tripled over that seen in Phase III trials.[20,21] As noted in Table 2, real-world cure rates from usual care are often substantially lower than predicted by Phase III studies, especially in treatment-experienced patients with cirrhosis. [22,23,24]

Table 2. Comparison of Sustained Viral Response in Phase III Studies and in Usual Care Settings

Treatment regimen	Phase III studies (SVR)	Usual Care (SVR)
PEG-IFN + RBV + Protease Inhibitor	70-75%	43-60%
PEG-IFN + RBV + Sofosbuvir	90%	80%[25]
Sofosbuvir + RBV	90%	69%[26]
Sofosbuvir + Simeprevir ± RBV	94%	88%[27]

PEG-IFN= pegylated interferon, RBV=ribavirin, SVR= sustained viral response rate

Dr. Jodi Segal and colleagues performed a systematic review of the oral regimens during the planning stage of this application.[28] None of the Phase III trials had active comparator groups; instead, these regimens were compared to historical control groups and compared within the trials to regimens modified by the addition or absence of ribavirin. A summary of SVR12 and confidence intervals from these Phase III trials is shown below. We illustrate here, simply, the wide and overlapping confidence intervals across regimens.



Several federally funded agencies and institutes have recognized the issues associated with these critical evidence gaps in HCV. In late 2014, the Patient-Centered Outcomes Research Institute (PCORI) convened a large stakeholder engagement meeting that included representatives from the pharmaceutical industry, patient advocacy groups, payers, patients and providers and concluded *"data are particularly needed on longer-term effectiveness of new therapies, on the comparative effectiveness of these therapies, and on a set of treatment outcomes relevant to patients, including symptoms of infection, drug side effects, treatment adherence, and quality of life"*. The Agency for Healthcare Research and Quality identified as top-tier research needs effectiveness designs to understand real-world effects of antiviral regimens in a broader spectrum of patients, such as those with co-morbid conditions and cirrhosis.[29] The Center for Evidence-based Policy at Oregon Health & Science University also identified many evidence gaps in the current studies that support treatment guidelines for HCV and concluded: "Policymakers can ask the NIH to fund and the FDA to demand truly comparative studies on this [Sofosbuvir] and other newer drugs for hepatitis C. Current trials do not answer the question of which therapy is best for which patient at which point in time during the disease course. Studies of these drugs should include populations that approximate the characteristics of publicly insured patients including race, stage of disease, prior treatment history, and comorbid medical and behavioral conditions."[30] As highlighted in the 2015 report from the Institute for Clinical and Economic Review (ICER),[31] "for the patient population with cirrhosis, the confidence intervals are wide for all four of the new DAA combinations. Pragmatic randomized trials in real-world settings will be essential for evaluating the comparative effectiveness of the combination DAA therapies and to see if the SVR achieved in clinical trials and long-term cure rates are replicated in usual care settings." Furthermore, since these data come from single arm studies, in which everyone enrolled in a trial receives the experimental therapy, selection bias may explain some of the observed differences among the SVR point estimates. Lastly, there also exist significant gaps in our understanding

of baseline viral resistance and how it impacts treatment outcomes. While almost every new therapy has known naturally occurring resistance, the clinical significance is poorly understood. Many of the current guidelines and drug labels include consideration for resistance testing prior to using oral therapies, but only one regimen recently approved from Merck has clear guidance on how to adjust therapy based on the presence or absence of resistant viral variants.[32, 33, 34]

Significance

The absence of comparative effectiveness data has led to restricted access to treatment as well as to payer-mandated use of specific regimens based on negotiated pricing. Patients with mild liver disease and those with recent alcohol or drug use are often excluded from treatment plans. The HCV marketplace has evolved in a manner that may hamper a simple, randomized, controlled pragmatic trial utilizing commercial drug supply. The limitations to treating patients in the real world are based on two ill-conceived principles: 1) Restrictions to the formulary for which drugs will be accessible under specific insurance plans and 2) Restrictions about which patients can be treated based upon the severity of liver disease or other more arbitrary factors such as history of substance abuse. Despite objections by many, including the AASLD/IDSA Guidelines Panel and The President's Advisory Council on HIV/AIDS, these have been imposed, without scientific rationale, solely to minimize cost to payers. Indeed, the preponderance of current evidence suggests that almost all patients with hepatitis C would benefit from treatment, with minimal harms and regardless of severity of liver disease. Furthermore, in clinical practice there appears to be treatments that would be better than others for certain subpopulations with comorbidities, yet by happenstance of socioeconomic status or geography, these medications are beyond the reach for many persons infected with hepatitis C. Thus, the choice of treatment and regimen has been removed from key stakeholders (patients and physicians). Also, important patient groups have been underrepresented in HCV clinical trials, including Black Americans, older adults, and persons with active substance use or mental illness, especially those with advanced liver disease. Through active engagement with HCV patient advocacy organizations and HCV patient partners, we learned that the top-ranked priorities to inform decisions about HCV treatment include: likelihood of being cured, out-of-pocket costs of therapy, drug side effects and other short and long-term treatment harms and benefits. Our pragmatic clinical trial is specifically designed to address these important study outcomes identified by multiple stakeholders. Importantly, the study will provide data on underrepresented populations (Black Americans, individuals with multiple comorbidities, low-income groups, older adults age > 65, individuals with substance use and mental health disorders) and subgroups (genotype 1a vs 1b) so the results of this study will be applicable to most clinical settings. We selected this subgroup because patients with cirrhosis have been under-represented in clinical trials (typically <15% of trial population) but comprise up to 50% of those who will be considering antiviral therapy. Moreover, those with cirrhosis are potentially more susceptible to short and long-term harms from the medications and have shown the largest difference in SVR when comparing real-world observational data with phase III trial results.[35] Recent post-approval safety concerns for both regimen H (cardiotoxicity with Amiodarone) and V (hepatotoxicity in advanced cirrhosis), highlight the critical need for safety data in larger, more diverse populations. Thus, our study will provide valuable information for all patients considering HCV treatment including this vulnerable subgroup (cirrhosis). This proposed study of new oral regimens is very responsive to this PFA and will answer critical questions regarding: 1) rates of patients being cured and durability of cure, 2) drug side effects and other short and long-term treatment harms, and 3) patient-centered clinical benefits (changes in patient-reported HCV symptoms) and short and long-term liver disease progression or regression.

The PRIORITIZE investigators have had extensive discussions with pharmaceutical manufacturers, payers, and pharmacy benefits managers to develop mechanisms that would ensure randomized access to medications. Unfortunately, most pharmaceutical sponsors and payers have little interest or incentive to develop evidence to refute the current restrictions. Market leaders are content with the status quo that

guarantees them garish profits and payers continue to control their costs, largely unchallenged by a disenfranchised patient population, which has been denied a voice in this discussion. Payers and pharmacy benefits managers have significant financial disincentives to randomize across all regimens, due to contractual discounts most have received to exclusively use one regimen over others. Similarly, despite enthusiastic and significant financial support for our observational cohort study (HCV-TARGET), pharmaceutical companies have been reluctant to support a randomized, controlled trial that could influence future policy and guideline decisions, and potentially threaten their market share/profits. Given these implications, Gilead did not agree to supply free study drug. Fortunately, AbbVie and Merck continue to support this trial, and the current design takes advantage of "free drug" to achieve our goal of a randomized, controlled trial. The decision of some pharmaceutical companies not to provide access to drugs for the trial underscores the importance of independent organizations in the effort to conduct comparative effectiveness studies. Indeed, we believe it is incumbent upon investigators and patient-centered research funding sources, therefore, to develop sound evidence to support or refute the current status of HCV treatment in order to optimize care for patients with chronic hepatitis C.

Impact on clinical practice: In 2011, we established a large, real world, observational treatment registry called HCV-TARGET to follow patients prescribed HCV therapy at multiple centers in the U.S., Canada, and Europe. Although HCV-TARGET continues to produce high-quality observational cohort data to rapidly inform clinical guidelines and enhance treatment safety and efficacy, we strongly believe that a well-designed randomized controlled trial is critical to impact practice and policy at the level needed to improve patient-centered outcomes for all HCV patient populations. These data will be instrumental for patients, physicians, payers and policy makers to make sound and rational treatment decisions. Comparative data from this study can inform clinical, policy and insurance guidelines so that cost is not used as the sole criterion to evaluate the interventions. Most importantly, the data can help patients and physicians make more informed treatment decisions. Through HCV-TARGET's existing partnership with the FDA, the FDA can use the data to monitor and act on differences in safety from what was reported during phase III trials or expand label indications. HCV-TARGET data has already been instrumental in identifying new safety signals (cardiovascular risk in patients taking Sofosbuvir), drug-drug interactions (proton pump inhibitors and Ledipasvir), and expanding drug labels (expansion of Simeprevir label to include all oral combination with Sofosbuvir). Our stakeholder organizations also will use their established relationships to share the study findings with state and federal representatives that influence public policy and coverage decisions. Further descriptions for dissemination of study results are detailed in the Dissemination and Implementation section.

Patient-centeredness: PCORI was established from the Affordable Care Act Legislation to address gaps in health care evidence that are important to patients, their families, and their providers. In response to the PCORI HCV Stakeholder meeting detailed earlier, a major HCV-specific funding initiative (PFA) was used to support this study. Core principles in PCORI funding are the inclusion of patient stakeholders (including their families, advocacy groups and providers) in the development, implementation, and dissemination of PCORI funded research. To that end, this study was developed over 1.2 yrs through active engagement with HCV patient advocacy organizations, HCV patient partners, and HCV providers among other HCV stakeholders. First, our investigative team conducted 45 interviews to discuss HCV treatment with patients infected with HCV who represent a diverse population (age range 35-72 with a mean age of 55, 58% male, 56% treatment naïve, 36% with cirrhosis, 20% Black American, 24% uninsured). Participants were asked to

TABLE 3

Priority Rank	HCV PEG Ranking of Reported Informational Needs
1st	Chance of cure
2nd	Total out of pocket cost of treatment
3rd	Treatment side effects
4th	Harm to my liver
5th	Harm to my other medical conditions
6th	Interference with functional status & QOL
7th	Long-term survival if cured
8th	Benefits to my other medical conditions
9th	Risk or harm if I do not do treatment
10th	Benefits to my functional status & QOL

free-list all information they needed to make an informed decision about starting HCV treatment or choosing between hypothetical regimens. These interviews helped us understand what kind of information was critical to patient decision-making. Next, we asked our 9-member HCV Patient Engagement Group (HCV-PEG) to prioritize these informational needs, all considered harms or benefits to the patients (see Table 3). These HCV-PEG priority rankings directly informed the selection of patient-centered outcomes we intend to evaluate in this trial. We learned that the top-ranked priorities to inform decisions about HCV treatment include: likelihood of being cured, out-of-pocket costs of therapy, drug side effects and other short and long-term treatment harms and benefits. This trial is specifically designed to address these important study outcomes identified by multiple stakeholders. Importantly, the study will provide data on underrepresented populations (Black Americans, individuals with multiple comorbidities, low-income groups, older adults age > 65, individuals with substance use and mental health disorders) and subgroups (genotype 1a vs 1b) so the results of this study will be applicable to most clinical settings. We selected this subgroup because patients with cirrhosis have been under-represented in clinical trials (typically <15% of trial population) but comprise up to 50% of those who will be considering antiviral therapy. Moreover, those with cirrhosis are potentially more susceptible to short and long-term harms from the medications and have shown the largest difference in SVR when comparing real-world observational data with phase III trial results.[36] Recent post-approval safety concerns for both regimen H (cardiotoxicity with Amiodarone) and V (hepatotoxicity in advanced, decompensated cirrhosis), highlight the critical need for safety data in larger, more diverse populations. Thus, our study will provide valuable information for all patients considering HCV treatment, including the cirrhotic subgroup.

This proposed study will answer critical questions important to patients with HCV regarding: 1) rates of patients being cured and durability of cure, 2) drug side effects and other short and long-term treatment harms, and 3) patient-centered clinical benefits (changes in patient-reported HCV symptoms) and short and long-term liver disease progression or regression.

3. PURPOSE AND SIGNIFICANCE

Phase 1

The original purpose of this study was to learn whether oral regimens for treating HCV worked equally well under real-world conditions when delivered to a broad spectrum of patients. The proposed study utilized a randomized pragmatic clinical trial design to compare the effectiveness of standard of care medications for HCV Genotype 1 (HARVONI®-Regimen H, Viekira Pak/Viekira XR™- Regimen V, and Zepatier™- Regimen Z). The study collected and analyzed comprehensive data to address the multi-faceted outcomes and measures that HCV patients and stakeholders identified as being most important when making HCV treatment decisions.

Phase 2 (As of January 2017 Amendment and May 2018)

The purpose of this study is to learn whether oral regimens for treating HCV work equally well under real-world conditions when delivered to a broad spectrum of patients. The amended study will utilize a randomized pragmatic clinical trial design to compare the effectiveness of standard of care medications for HCV Genotype 1 (HARVONI®-Regimen H and Zepatier™- Regimen Z). The study will collect and analyze comprehensive data to address the multi-faceted outcomes and measures that HCV patients and stakeholders identified as being most important when making HCV treatment decisions. In consideration that there are no changes to safety or efficacy of Viekira™, participants randomized to Viekira™ in Phase 1 of this study will remain on Viekira™ and continue to be followed.

4. STUDY DESIGN

The proposed study will compare the effectiveness of approved, HCV Genotype 1 treatment regimens to learn whether they work equally well under real-world conditions. Using methods developed in HCV-TARGET to collect clinical data on safety and effectiveness, patients receiving HCV therapy in community and academic clinics will be offered the opportunity to consent to be randomly assigned to Regimen H, V, (Phase 1) or Z, and then observed for outcomes. Once randomized, all medical care, laboratory testing, and any disease or side effect management will be assumed by usual care conditions, in keeping with pragmatic design principles. The collection of patient reported outcomes (PRO) surveys is atypical in standard clinical care; therefore, to preserve the usual clinical conditions and pragmatic design principles, the PRIORITIZE PRO surveys will be administered through the use of technology /devices outside of clinical interactions (web-based and phone based surveys). We received extensive patient and stakeholder input in designing this trial to yield results that will be useful to patients, clinicians, payers, and policy makers when making decisions about treatment. These study aims directly target the majority of informational needs and evidence gaps identified by HCV patients, clinicians, multiple stakeholders, the Agency for Healthcare Research and Quality CER systematic review, and PCORI's Working Group on HCV.

Phase 1

We originally proposed a pragmatic, open-label, randomized study of **approximately 3750** participants that will allow evaluation of HARVONI®, Viekira Pak/Viekira XR™ and Zepatier™. The proposed study design assumed HARVONI® (H) would only be available via commercial payer while Viekira Pak/Viekira XR™ (V) and Zepatier™ (Z) would be provided by the manufacturers. AbbVie and Merck agreed to provide free drug and to set up drug delivery protocols with our centralized pharmacy. Additionally, Merck provided free NS5a (Resistance Associated Polymorphisms) RAP testing for all patients participating in the study. The results of the RAP testing for genotype 1a participants randomized to ZEPATIER™ were used clinically to determine treatment regimen; with those without RAPs (approx. 90%) were provided 12 weeks of Z, while those with RAPs were provided 16 wks + RBV (per FDA label recommendations). NS5A RAP testing for patients on other regimens were used for research purposes only.

Phase 2 (Amendment as of January 2017 and May 2018)

The second phase of this study will follow the amended protocol and will continue as a pragmatic, open-label, randomized study of **n= 1700** (estimated) consented participants that will allow evaluation of at least 1228 patients who begin treatment with HARVONI® and Zepatier™. The N assumes enrollment/randomization of 154 subjects to Viekira™ in Phase 1 (146 began treatment), at least 707 subjects randomized to Harvoni® with at least 375 starting therapy, and up to 730 subjects randomized to Zepatier™ to achieve at least 707 starting therapy. The proposed study design assumes HARVONI® (H) will only be available via commercial payer while Zepatier™ (Z) will be provided by the manufacturer. Merck has agreed to provide free drug and has set up drug delivery protocols with our centralized pharmacy. Additionally, Merck will provide free NS5 (Resistance Associated Polymorphisms) RAP testing for all patients participating in the study. The results of the RAP testing for genotype 1a participants randomized to ZEPATIER™ will be used clinically to determine treatment regimen; those without RAPs (approx. 90%) will be provided 12 weeks of Z, while those with RAPs will be offered 16 wks + RBV (per FDA label recommendations). NS5 RAP testing for patients on other regimens will be used for research purposes only.

Sample Size Rationale

For the primary analyses comparing regimens H and Z, the ITT analysis will be modified to use causal inference methods to address potential selection biases induced by the Harvoni arm of the study --due to

Harvoni's arduous prior authorization hurdles such as requirement for negative urine toxicology tests and denial of persons with minimal fibrosis. In total, we anticipate that about N = 1700 participants will be consented and enrolled, with at least 1228 being both successfully randomized and successfully starting treatment as follows: 1228 = (707 to Z) + (375 to H) + (146 to V). Due to the discontinuation of assignments to regimen V, only 154 enrollees were assigned to regimen V. Of those, only 146 started V regimen treatment. While equal numbers of participants are assigned by randomization to H and Z, the sample size expectations take into account the higher rate of failure to start treatment that is inherent for those assigned to regimen H (see Section 13. Statistical Analysis Strategy).

The **Primary Aims** are to characterize and compare regimens H, V (Phase 1), and Z on the following patient-centered outcomes:

1) treatment effectiveness (i.e., sustained viral response 12 weeks post-treatment, "SVR12")
2) drug side effects. (both patient reported and medical record abstracted)
3) efficacy of ZEPATIER™ with RBV for 16 weeks when used in G1A patients with baseline RAPs

The **Secondary Aims** are to characterize and compare regimens H, V (Phase 1), and Z on the following outcomes:

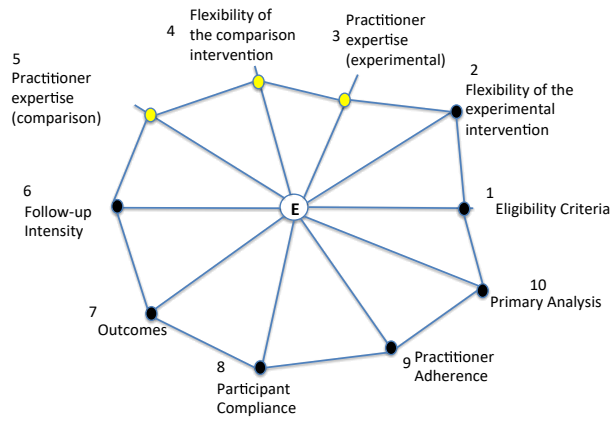
3) treatment adherence and persistence;
4) amelioration of systemic HCV-associated symptoms post-treatment;
5) post-treatment progression and regression of liver disease
6) persistence of viral cure for 3 years post- treatment; and
7) functional status on treatment and after treatment.
8) impact of baseline NS5A RAPs on treatment outcomes

The **Expected Results**

1) In clinical practice populations, the regimens will have similar cure rates and durability of cure.
2) The frequency and severity of drug side effects may be higher for regimens that are more likely to require concomitant use of ribavirin, V (Phase 1) more than H or Z
3) Medication non-adherence may be greater for regimens that have higher pill burden and more frequent side effects from DAA alone or from requirement for concomitant use of ribavirin, V more than H or Z
4) After achieving SVR, improvements will be evident in measures of clinical outcomes (incident cancer, liver decompensation, and/or diabetes) and systemic HCV symptoms.
5) After achieving SVR, improvements will be evident in measures of liver disease (fibrosis and progression to cirrhosis).
6) After achieving SVR, the incidence of new or latent HCV infection will be extremely rare.
7) After achieving SVR, improvements will be evident in functional status.
8) SVR in genotype 1a patients with RAPs will be similar regardless of previous treatment experience and or cirrhosis status

Appropriateness of a Pragmatic Design for this Study

The proposed study will compare the effectiveness of 3 approved HCV treatment regimens to learn whether they work equally well under real-world conditions. Using methods developed in to collect clinical data on safety and effectiveness, patients receiving HCV therapy in community and academic clinics will be offered the opportunity to consent to be randomly assigned to Regimen H, V (Phase 1), or Z and then observed for outcomes. Once randomized, all medical care, laboratory testing, and any disease or side effect management will be assumed by usual care conditions, in keeping with pragmatic design principles. A pragmatic-explanatory continuum indicatory summary (PRECIS) exercise was undertaken; we found our proposed study to be highly pragmatic.



PRECIS Summary: A. The participants will receive the standard clinical care that is delivered in their respective center for the treatment of HCV; **the clinical management, visit schedule, and safety and efficacy lab evaluation schedule is not defined by the protocol.** B. All data related to that standard clinical care will be abstracted from submitted medical records (clinic notes, telephone notes, safety and efficacy labs) by a specially trained group of chart data abstractors. C. The collection of patient reported outcomes (PRO) surveys is atypical in standard clinical care; therefore, to preserve the usual clinical conditions, PRO surveys will be administered through the use of technology / devices outside of clinical interactions (web-based and phone based surveys). *The Yellow wheel plots indicate design options that move away from the Pragmatic pole toward the explanatory design pole.*

Study design: For a broad population of individuals seeking treatment for HCV genotype 1, we propose a multi-center, three-arm, randomized pragmatic clinical trial to compare Regimen H (n ≥ up to 730 randomized to achieve at least 375 dosed) Ledipasvir / Sofosbuvir (HARVONI®, Gilead Sciences) vs Regimen V (up to 170) Paritaprevir/ritonavir/ Ombitasvir + Dasabuvir +/- ribavirin (Viekira Pak/Viekira XR™, AbbVie) (Phase I) vs Regimen Z (n ≥ up to 730 randomized to achieve at least 707 dosed) Elbasvir/Grazoprevir (ZEPATIER™Merck & Co). Using the HCV-TARGET infrastructure for data collection with the addition of patient surveys for collection of patient-reported outcomes and a validated model for impact on liver disease progression, the study is open-label for both participants and providers.

Study population and proposed inclusion and exclusion criteria: All patients infected with HCV genotype 1 being considered for HCV therapy will be invited to consent to have their HCV treatment and outcomes observed. Among the patients who consent to be observed, most will meet inclusion criteria to participate in The Randomized Cohort: a) in the provider's opinion, the patient can begin treatment with regimen H, V(Phase I), or Z without significant risk or harm and b) the patient is willing to consent to have their HCV treatment assigned randomly. We anticipate some participants (up to 21%) may **not** receive treatment with their randomized regimen. These 5%-10% include participants who decide to choose a different regimen after being randomized and participants who cannot gain access to the commercially available regimen (HARVONI®) when assigned. Randomization will be stratified by cirrhosis status (based on biopsy or markers of cirrhosis) and by subtype 1a or 1b. Stratification by cirrhosis is important in assessing SVR and clinical outcomes and fibrosis progression/regression while stratification by subtype is important as this impacts the need for RBV, adherence and tolerance. Genotype 1a participants randomized to ZEPATIER™ will have their baseline NS5a RAP sample tested prior to dispensing drug. If a baseline RAP at amino acid positions 28, 30, 31, and/or 93 is identified, those genotype 1a patients will be offered ZEPATIER™ for 16 wks + RBV, consistent with the FDA label recommendation.

Our approach will build on the HCV-TARGET infrastructure for data collection with the addition of patient surveys for collection of patient-reported outcomes and a validated model for impact on liver disease progression. PRIORITIZE will be implemented using the fully functional HCV-TARGET infrastructure and committed clinical sites. HCV-TARGET is rooted in the collaborative network developed through the National Institutes of Health's Clinical and Translational Science Award program. The registry follows patients treated for chronic HCV to rapidly inform strategies for better management of populations underrepresented in clinical trials and to identify and remediate educational gaps relative to

treatment guidelines and adverse event management. HCV-TARGET has grown into an extensive partnership between 42 academic and 14 community centers (in 31 states, Puerto Rico, Canada and Europe), the pharmaceutical industry, HCV community advocates and the FDA. HCV-TARGET developed standardized, centralized chart data abstraction methods along with detailed data monitoring to increase the efficiency and quality of an observational registry while also minimizing costs typically associated with performing post-marketing clinical research.

4.1 Study Infrastructures and Centers

The PRIORITIZE study will be led by co-PIs at three universities: David R. Nelson, M.D., at the University of Florida (UF- Clinical Coordinating Center); Michael Fried, M.D. & Donna Evon, Ph.D. at the University of North Carolina (UNC- Data Coordinating Center); and Mark Sulkowski, M.D., at Johns Hopkins University. Additional experts at each of the three universities as well as the University of Michigan (fibrosis progression modeling) will contribute to the project. In addition, the PRIORITIZE study will utilize the operational infrastructure of the existing HCV-TARGET Research Network. UF serves as the Clinical Coordinating Center (CCC) and UNC serves as the Data Coordinating Center (DCC) for HCV-TARGET; they will perform the same roles for PRIORITIZE.

PRIORITIZE will be implemented using the fully functional HCV-TARGET infrastructure and up to 45 committed clinical HCV-TARGET sites. HCV-TARGET developed standardized, centralized chart data abstraction methods along with detailed data monitoring to increase the efficiency and quality of an observational registry while also minimizing costs typically associated with performing post-marketing clinical research. The HCV-TARGET sites were selected for their historical enrollment patterns, contributions to the network and based on the HCV drug prescription market analysis that was used to identify centers with high approval percentage for HARVONI® prescription.

5. SUBJECT POPULATION

5.1 Inclusion criteria

- HCV Genotype 1a or 1b, Adult patients (age 18 or older) who are being prescribed HCV treatment outside of a clinical trial and, in the provider's opinion, can begin treatment with regimen H, V (Phase 1), or Z

5.2 Exclusion criteria

- Inability to provide written informed consent
- HARVONI® is not a covered drug on benefits formulary
- Current or historical evidence of hepatic decompensation (variceal bleeding, hepatic encephalopathy, or ascites). In the event potential participant is post-transplant, no evidence of hepatic decompensation since transplantation
- Child Pugh (CTP) B or C Cirrhosis (documented CTP calculation is required)
- Pregnant or breastfeeding women

6. HCV-TREATMENT PRODUCTS

6.1 Investigational New Drug (IND) Exemption

Given that the study drug regimens used in PRIORITIZE are marketed drugs at the time included in the randomization schedule and in accordance with 21 CFR 312.2(b)(1), PRIORITIZE will be IND exempted. While this exemption from the standard methods of providing clinical trial data to the FDA is

expected, a less traditional but perhaps more efficient communication of the details of the clinical trial between the FDA and PRIORITIZE will be employed. Via a memorandum of understanding, the research team has partnered with FDA to share data on how newly approved therapies for hepatitis C are used and managed in routine practice. Through this unique partnership, research members will be able to evaluate how marketed drugs are used and managed in routine practice. Through this distinctive partnership, PRIORITIZE will continue to disseminate important safety, efficacy, and general characteristics of the HCV patient population to the FDA and drug manufacturers from the PRIORITIZE trial.

6.2 Provision of HCV drug

In late July 2016, the FDA approved a once daily dosing formulation of Paritaprevir/ritonavir/ Ombitasvir + Dasabuvir, Viekira XR. Viekira XR™ was approved by the FDA for use in the HCV Genotype 1 population. Patients participating in PRIORITIZE Phase I will have either Viekira Pak™ or Viekira XR™ made available for treatment to arm V of the study. While subjects will no longer be randomized to Viekira™ during Phase 2 of this study, participants randomized to Viekira in Phase 1 of this study will be maintained on the Viekira™ dosing formulation to which they were initially dispensed.

Commercially labeled HCV product for Viekira Pak/Viekira XR™(Phase 1) and Zepatier™ +/-RBV will be provided *free of charge* to PRIORITIZE study participants randomized in non-VA sites to those regimens by AbbVie and Merck. Participants randomized to HARVONI® will have their respective HCV treatment prescription processed and filled through standard payer processes.

6.3 Rationale Provision of HCV drug

PRIORITIZE is a pragmatic study with HCV-treatment duration, addition of ribavirin to the treatment regimen and treatment/side effect management all decided at the discretion of the local provider according to the site standard of care and is not defined by this protocol. Given the pragmatic design of this study, ideally the randomized HCV drug would be acquired from the usual and customary clinically prescribed therapy sources. However, current market HCV prescribing practices in most payer systems have been limited by payer exclusive product contracting. A detailed market simulation was performed in August 2015 to evaluate HARVONI® and Viekira Pak™ prescription rejection rates of 43 current HCV-TARGET sites including the 35 centers proposed to participate in the PRIORITIZE study. Based on that analysis, there is a rejection variance depending on health care center. The overall median rejection rate for HARVONI® prescription was 11% with a range of 0-26% (excluding a single outlier that had a 46% rejection rate) while the median rejection rate for Viekira Pak™ prescriptions was 68% (range 32-91%). Parity between the two regimens (ability to prescribe both H and V) was evident only 10% of the time (range 0%- 32%). This simulation supports wide availability of HARVONI® by prescription, high rejection rates of prescribed Viekira Pak™ and very limited ability to prescribe both drugs among HCV-TARGET centers. In addition, the very recent approval of Zepatier™ and lengthy contractual procedures for restructuring pharmacy contracts suggest that Zepatier™ will have limited uptake over the next year. These data demonstrate the challenging environment for a randomization design that utilizes real world access to each regimen and has informed our approach to develop the best possible study design.

With wide availability of HARVONI® by prescription and provision of free drug from AbbVie and Merck to treat patients in PRIORITIZE, the cohort for enrollment into this study will be limited to patients whose insurance formulary has HARVONI® as a covered drug (approximately 90% of all insured HCV patients), except patients in the Veterans Health Affairs Administration. This will include most commercial payers (Aetna, Anthem, BlueCross, Cigna, Humana, and United healthcare), most PBMs

(BioPlus, CVS Caremark, EnvisionRx, Kroger Specialty Pharmacy (formerly known as TLCRx), PBM Prime Therapeutics), and Medicare Part D.

Phase 2

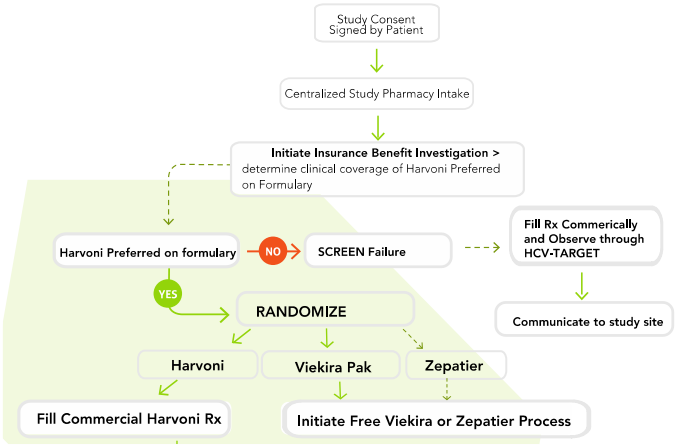
- Viekira™ (one of the three standard of care treatments for HCV that is being studied) will be replaced in the market by the approval of AbbVie's next generation compound during the planned enrollment phase for PRIORITIZE. This has and will continue to negatively impact enrollment and make future data on the results for the Viekira™ arm not relevant.
- **Background:** Glecaprevir (ABT-493)/pibrentasvir (ABT-530) (G/P) is an all-oral, once-daily, ribavirin-free investigational hepatitis C virus regimen from AbbVie. Recently released phase 3 trial data show excellent response in genotype 1 patients. Overall, 99% of non-cirrhotic patients reached SVR_{12} after 8 weeks of treatment (n = 348); 96% in those with compensated cirrhosis with 12 weeks of therapy. It has received "breakthrough" designation by the FDA and is expected to be approved in the US in summer 2017. As a result of the anticipated approval, the once daily, ribavirin-free G/P regimen will replace Viekira™ in the United States and Viekira™ will eventually be removed from the US market.
- Given that there are no changes in the safety or efficacy of Viekira Pak/XR™, each patient who has been randomized to Viekira (n=154 randomized with n=146 dosed), will complete their assigned regimen and remain in the study for long-term follow-up. No further patients will be assigned to Viekira™. Further recruitment and balanced randomization to Harvoni® and Zepatier™ will ensure that up to 1,460 patients are randomized to those two regimens. At the end of the study, the primary analyses characterizing and comparing Harvoni® and Zepatier™ will be based on at least 1082 patients starting treatment (375-H, 707-Z). Of secondary importance, the primary analyses (descriptive) concerning Viekira will be based on the first 510 patients (up to 170).

6.4 Centralized Study Dispensing Specialty Pharmacy- Participants outside the Veterans Health Administration

Phase 1

A full service, experienced specialty pharmacy (Kroger) will be used as a centralized pharmacy to manage the HCV treatment prescriptions for participants outside of the Veterans Health Administration. After signing consent, patient-specific prescriptions for HARVONI®, Viekira Pak(V)/Viekira XR™ (Phase 1) and Zepatier™ will be submitted to the centralized specialty dispensing pharmacy to initiate an *insurance benefit investigation*. If the benefits investigation identifies HARVONI® as a covered drug on the respective patient formulary, the patient will be RANDOMIZED to receive either *HARVONI® by prescription* or *Viekira Pak/Viekira XR™* (Phase 1*) or Zepatier™* via the free drug provided by AbbVie/Merck (see Centralized Pharmacy Study Enrollment Process). If the benefits investigation identifies any non-HARVONI® regimen as preferred, the patient will be counted as a SCREEN FAILURE and will not be randomized. This patient may be offered the opportunity to be followed for outcomes in the observational HCV-TARGET study that runs in parallel to PRIORITIZE as an observational cohort.

CENTRALIZED PHARMACY STUDY ENROLLMENT PROCESS



Phase 2
A full service, experienced specialty pharmacy (Kroger) will be used as a centralized pharmacy to manage the HCV treatment prescriptions for participants outside of the Veterans Health Administration. After signing consent, patient-specific prescriptions for HARVONI® and Zepatier™ will be submitted to University of Florida and Kroger, the centralized specialty dispensing pharmacy. Initial benefit assessment can be performed by the institution or the Kroger Specialty Pharmacy. Participants will be RANDOMIZED to receive either *HARVONI® by prescription* or *Zepatier™* via the free drug provided by Merck. If the benefits investigation identifies any non-HARVONI® regimen as preferred, the patient will be counted as a Randomization Failure and will not receive HCV treatment through this protocol. This patient may be offered the opportunity to be followed for outcomes in the observational HCV-TARGET study that runs in parallel to PRIORITIZE as an observational cohort.

Aside from free drug provided by AbbVie (Phase 1) and Merck, PRIORITIZE participants will have access to the full slate of services provided by specialty pharmacy to mimic as closely as possible the real-world experience of HCV-treatment. The centralized study pharmacy will work directly with PRIORITIZE patients to dispense drug and maintain drug refills, provide access to on-staff clinical pharmacists, and on treatment support consistent with standard specialty pharmacy practices. Additionally, patients randomized to receive HARVONI® which will be dispensed via the usual and customary clinically prescribed therapy sources, the centralized specialty pharmacy will provide to the sites and patients their resources to maximize third party reimbursement, coordination of prior authorizations and appeals, expertise in formulary overrides, and support to access drug co-payment cards. Patients randomized to ZEPATIER™ will have their baseline NS5a RAP sample tested prior to dispensing drug. If a baseline RAP at amino acid positions 28, 30, 31, and/or 93 is identified, those patients will be offered ZEPATIER™ for 16 wks + RBV, consistent with the FDA label recommendation.

6.5 HCV Therapy Prescription Cost for Patients who are randomized to HARVONI®

Patients randomized to HARVONI® will potentially have drug co-pays while those randomized to Viekira Pak/Viekira XR™ (Phase 1) or ZEPATIER™-will not have a co-pay. Kroger Specialty Pharmacy has indicated HARVONI® therapy co-pays can range from $5-$1000, depending on insurance benefit. The centralized study pharmacy is providing resources to help and guide patients to obtain access to HARVONI® co-pay assistance cards, which reduces the co-pay to $5 and should minimize this impact. Although there is a co-pay disparity between the two randomized groups, because we are selecting a cohort of patients with HARVONI® preferred on formulary, these patients are receiving the treatment by

prescription they would have otherwise received as part of standard of care and thus also have the same co-pay burden they would have as part of standard of care. We have consulted with our UF legal department and IRB, who concluded that the design and randomization is in compliance with the Common Rule.

6.6 HCV Therapy Prescriptions for Patients who cannot have Commercial Product dispensed through the Centralized Specialty Pharmacy

It is recognized that the centralized specialty pharmacy may not be able to fill all commercially acquired prescriptions for patients randomized to the HARVONI® arm of the study. The centralized specialty pharmacy will provide the insurance benefits verification information to the study site as well as forward to the respective payer-approved pharmacy to complete the commercial HARVONI® product dispensing for HCV treatment. That patient will continue to be followed in PRIORITIZE for all outcomes.

6.7 HCV Therapy Prescriptions for Screen Failure and Randomization Failures

The centralized specialty pharmacy will communicate back to the study site the status of patients submitted for the insurance benefits investigation. For study participants who screen fail or do not begin treatment with their respectively randomized regimen (randomization failure), it will be at the discretion of the study site to determine how to proceed with treating that patient. All efforts will be made to follow randomization failures in PRIORITIZE. In the event participants begin treatment with a medication other than H or Z, these participants may be enrolled in HCV-TARGET database to capture the treatment course and outcomes.

7. STUDY PROCEDURES

7.1 Informed Consent

The protocol and informed consent documents will receive approval by the local site IRB prior to initiation of the study at each site. Consent for participation in PRIORITIZE will include permission 1) to submit historical medical records related to patient demographics, medical/co-morbid condition history, prior HCV therapy and evaluation of liver disease, 2) to submit prospective medical records related to HCV treatment response, safety, side effects, side effect management and safety/efficacy outcomes of antiviral therapy; 3) for collection of patient reported symptoms and outcomes via surveys administered via paper, online or by telephone outside of the standard clinical interaction; 4) to be followed for HCV systemic symptoms, co-morbid conditions, hepatic fibrosis progression/regression and mortality for up to 3 years after treatment outcome is determined; and 5) to share contact information to complete study surveys and social security number information to receive payment for survey completion. Subject contact information will be used for long- term follow-up by telephone or email for any participants who do not return to their local site for health care follow-up up to 3 years after HCV treatment 6) to have blood drawn for baseline NS5a RAP testing 7) to share limited datasets with PRIORITIZE research partners. Eligible participants being prescribed HCV treatment may be offered the opportunity to consent to participate in PRIORITIZE.

Written informed consent must be obtained before patient information is submitted for randomization.

Where approved by local IRBs, the investigator or qualified designee will explain the Future Biomedical Research to the subject. Subjects are not required to participate in the Future Biomedical Research. Subjects who decline to participate will not be discontinued from the main study and will have blood destroyed. Investigator or designee will answer all subjects' questions and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. Consent for Future Biomedical Research may be included in the main informed consent or a separate informed consent as per local IRB regulations or requirements.

7.2 Schedule of Observations and Schedule of PRO Assessments-

The schedule of observations is a **guide** for the HCV treatment data that is collected in PRIORITIZE and is provided in Table 4. HCV treatment is not dictated by the protocol. Dosing, treatment/side effect management, and duration will be at the discretion of the site/provider according to the site standard of care. Efficacy and safety outcomes observations (clinically documented drug side effects, clinical labs) as well as long term follow-up measures (disease progression/regression, mortality, co-morbid conditions) as part of the participants' standard clinical follow up and will be submitted and analyzed where available. Participants should be managed for HCV treatment and follow-up according to their respective local standard of care.

TABLE 4: SCHEDULE OF OBSERVATIONS *No window historically for baseline records submitted for Abstraction (Most recent records should be provided)

Assessments	**Screening & Randomization**	**Baseline**	**ON TREATMENT OBSERVATIONS through Follow-up**	**SVR/viral outcome**	**3 yrs after treatment baseline[b]**
Informed Consent	X				
Randomization	X				
Demographics		X			
Medical History/Co-morbid conditions		X			
Fibrosis Staging- all methods applicable		X			
Prior HCV Treatment Response, if applicable		X			
IL-28B genotype		X			
HCV Genotype (most recent genotyping)		X			
CBCD/Coags		X	Submit ALL CBCD results/reports collected during treatment through viral outcome.		
Serum Chemistries		X	Submit ALL chemistries to monitor patient health and safety during treatment through viral outcome.		
HCV RNA		X	Submit ALL HCVRNA results collected during treatment and Follow-up until SVR outcome is determined X		
Blood draw for HCV Resistance Associated Polymorphisms (RAP) testing	X[a]		X[c]		
Blood for Future Biomedical Research	X				
HCV Medications		X	Submit ALL clinic/telephone notes during treatment through viral outcome. Medication data to be abstracted from notes.		
ConMeds		X	Submit ALL clinic/telephone notes recorded during treatment through viral outcome. - conmed data to be abstracted from notes		
Adverse Events/Drug Side Effects			Submit ALL clinic/telephone notes recorded during treatment through viral outcome. - adverse event/drug side effect data to be abstracted from notes		

Year of Transplant (if transplanted)		X			
Progression of Liver Disease/Morbidity/Mortality[c]		BMI, labs, imaging (US/CT/MRI), liver stiffness measurement by Fibroscan, and histology to be submitted where done clinically according to data submission milestones. Data will be used to run disease progression modeling (Section 6.6)			

[a] – RAP testing will be performed on all Genotype 1a participants randomized to ZEPATIER™ prior to treatment initiation
[b] Yr 3- all hepatology records and labs from viral outcome to 3 yrs post baseline to evaluate disease progression/regression, alive/dead
[c] Participants with virologic failure may be asked to submit a sample for analysis of treatment emergent RAPs.

TABLE 5: PATIENT REPORTED OUTCOMES SCHEDULE OF ASSESSMENTS

Study Outcome	Measure	Baseline	Week 4	EOT	1 yr after treatment	3 yrs after treatment
Systemic HCV Symptoms	PROMIS Fatigue, Cognitive Impairment, Sleep Disturbance, Nausea, Diarrhea, and abdominal pain	X			X	X
Patient Reported Drug Side effects	PROMIS Fatigue & Nausea; Headache Impact Test (HIT)	X	X	X		
Functioning	HCV-PRO	X	X	X	X	X
Adherence / Persistence	3 Item Voils Survey, persistence rate		X	X		
Disease progression/mortality	Patient medical record & telephone call	X			X	X

Data related to standard clinical care, HCV treatment, drug side effects/adverse events, disease progression/regression, long term durability of SVR, co-morbid conditions and mortality will be abstracted from submitted medical records (clinic notes, telephone notes, safety and efficacy labs- see SCHEDULE OF OBSERVATIONS) by a specially trained group of chart data abstractors at the University of Florida. The collection of patient reported outcomes (PRO) surveys is atypical in standard clinical care; therefore, to preserve the usual clinical conditions, PRO survey will be administered through the use of technology / devices outside of clinical interactions (web-based and phone based surveys).

7.3 Baseline NS5 Resistance Associated Polymorphism (RAP) Testing

ALL participants, regardless of assigned treatment regimen, will undergo baseline NS5a resistance associated polymorphism testing **free of charge** via a central commercial laboratory vendor. The results of RAP testing can be used clinically to determine treatment duration and the addition of ribavirin to the regimen in support of the ZEPATIER™ US FDA label. Participants randomized to ZEPATIER™ will have their baseline NS5a RAP sample tested PRIOR to dispensing drug. If a baseline RAP at amino acid positions 28, 30, 31, and/or 93 is identified, those participants will be provided with 16 wks of ZEPATIER™ + RBV, consistent with the FDA label recommendation for resistance guided therapy. There are no label specific RAP testing recommendations for HARVONI® or Viekira Pak/Viekira XR™ (Phase I), thus participants randomized to HARVONI® or Viekira Pak/Viekira XR™ (Phase I), will be treated according to the prescribed local standard of care.

The baseline RAP testing sample will be collected PRIOR to dosing with HARVONI®, VIEKIRA PAK/VIEKIRA XR™ (Phase I), or ZEPATIER™. *Participants will not be charged for sample collection or NS5a RAP testing.*

7.4 Clinical Data- Baseline, On Treatment, Post-Treatment, and Long- Term Follow-up

Several clinical and laboratory evaluations are routinely performed in the management of HCV treatment and as part of standard clinical long-term patient follow-up. Medical records will be submitted to collect patient pretreatment variables (baseline characteristics), on treatment experience (for safety and efficacy) and the post-treatment experience (for safety and efficacy, disease progression/regression, co-morbid conditions, and mortality).

7.4.a Baseline demographic information

- Year of birth
- Gender
- Race
- Ethnicity (Hispanic or non-Hispanic)
- Weight
- Height (BMI will be calculated in database from provided Wt./Ht.)
- Insurance Type

7.4.b Baseline Clinical Data

Pre-treatment medical records, where available, containing the following information should be submitted to support centralized chart data abstraction.

- Prior treatment status will be ascertained as either naïve to therapy or treatment-experienced. Among treatment-experienced participants, prior response will be recorded in addition to therapies received that may be noted in the submitted medical records.
- Absence/Presence of cirrhosis and supporting diagnostic data. Site will submit any available information in the medical record obtained as part of standard of care (e.g., for diagnosis or follow-up) to evaluate hepatic fibrosis including:
  - **a.** most recent liver biopsy pathology report (fibrosis stage and staging method)
  - **b.** fibroscan/liver elastography report
  - **c.** serum fibrosis marker test results
  - **d.** most recent abdominal imaging (ultrasound, CT, or MRI)
  - **e.** or any test results to support calculation of fibrosis (i.e. FIB-4, APRI).
- Measures of portal hypertension
  - EGD report
  - Abdominal imaging (can also be used for fibrosis staging)
- Year of kidney and/or liver transplant (if applicable)
- Concomitant medications
- Key medical history/co-morbidities
  - Psychiatric disease
  - Diabetes mellitus
  - Cardiovascular or cardiac disease/conditions
  - Lipid disorders
  - Neurological disorders
  - Pulmonary diseases/conditions
  - Substances that contribute to co-morbid conditions (current or historical smoking, alcohol and substance abuse)
  - Coagulation disorders

- Prior/Current Malignancies including Hepatocellular carcinoma
- Chronic skin disease, including dermatologic extrahepatic manifestation of CHC
- HIV or HBV coinfection
- Other forms of liver disease (i. e. hemochromatosis, NASH)
- Pre-existing complications of liver disease if present or being treated at baseline (ascites, encephalopathy, esophageal varices).

7.4.c Baseline Laboratory Data

Where a result is available, the site will submit medical records that were collected as part of the site standard practice for participants undergoing HCV treatment. *Results must have been collected on or before the HCV treatment start date to be considered baseline. Submit laboratory results collected closest to the treatment start date.*

- HCV RNA level. This BASELINE value will be used to calculate change in HCV RNA during therapy.
- HCV RNA genotype and subtype
- HCV Resistance Mutation Testing (NS3/4, NS5a, NS5b)
- *IL28B* genotype (any historical result, if available)
- Complete blood cell count including platelets
- Measures of hepatic disease and function
- Measures of renal disease and function
- Measures of metabolic risk factors (i.e. fasting glucose, Hgb A1c)
- Prothrombin time/INR
- Results of Baseline Resistance Associated Polymorphisms (RAP) testing (if applicable)

7.4.d On-Treatment Clinical Data

On-treatment visits will coincide with local standard of care visits for participants in PRIORITIZE. Sites will submit medical records to document HCV treatment safety and efficacy. To support comprehensive centralized chart data abstraction of HCV treatment safety and efficacy, ALL on-treatment clinic notes and nursing/staff telephone notes will be submitted.

- **HCV Treatment Data**

  HCV-Therapy Regimen

  1. All anti-HCV therapies used (product names for each anti-HCV product used in the treatment regimen)
  2. Doses (starting doses of all products)
  3. Dose changes (any adjustments during treatment)
  4. Reasons for dose adjustments/premature discontinuation
  5. Treatment end date
  6. Duration of treatment

- **Adverse Events /Interval Complications of Liver Disease**

  ALL adverse experiences recorded in the medical record during treatment for HCV will be abstracted. Records documenting newly diagnosed hepatocellular carcinoma, ascites (radiologically verified), esophageal varices, and/or hepatic encephalopathy should also be submitted.

- **Liver Transplant**

Participants may require liver transplantation during HCV treatment or follow-up either as part of pre-treatment listing or due to HCV treatment complications. Records showing the date of transplant and reason for transplant will be submitted

- **Concomitant medications**

  ALL concomitant medications (over the counter and prescription) recorded in the medical record during the treatment for HCV or follow-up may be abstracted.

- **Laboratory data collection during treatment**

  To support comprehensive centralized chart data abstraction of HCV treatment safety and efficacy, ALL labs collected during HCV treatment to monitor safety and efficacy will be submitted. These include but are not limited to
  - Complete blood cell count including platelets
  - Measures of hepatic disease and function
  - Measures of renal disease and function
  - Measures of other organ disease and function
  - Prothrombin time/INR
  - HCV RNA levels

7.4.e Post Treatment Clinical and Laboratory Data

Post treatment visits will coincide with local standard of care visits for participants in PRIORITIZE. Sites will submit medical records to document HCV post treatment safety and efficacy. To support comprehensive centralized chart data abstraction of HCV post treatment safety and efficacy, **all clinic notes, telephone notes and lab results done to monitor the participants HCV treatment and outcome should be submitted through viral outcome**. If a patient does not physically return for a visit to the treating clinic in the immediate post-treatment period, a nursing/telephone note or equivalent source record should be submitted to document this. Additional medical records documenting hepatic decompensation (new/worsening ascites, encephalopathy, esophageal variceal bleeding) OR other events of special interest may be requested from the site to fully characterize HCV treatment safety outcomes.

- Complete blood cell count including platelets
- Measures of hepatic disease and function
- Measures of renal disease and function
- Measures of other organ disease and function
- Prothrombin time/INR
- HCV RNA levels

7.4.f Virologic Failure Resistance Associated Polymorphism (RAP) Testing

Any participant who exhibits virologic failure, regardless of assigned treatment regimen, may be asked to undergo resistance associated polymorphism testing for treatment emergent RAPs **free of charge** via a central commercial laboratory vendor. Virologic failure RAP testing samples must be collected within 30 days of known viral failure noted as part of standard clinical care (non-response, viral breakthrough, or relapse). In the event significant RAPs are identified in a failure test sample, blood collected at screening for NS5a testing may undergo additional RAP testing. *Participants will not be charged for sample collection or RAP testing.*

7.4.g Clinical Data Abstracted post HCV treatment and during Yr 3

Participants who return to the clinical site for annual follow-up after HCV treatment is completed will be followed for long-term health outcomes for up to 3 years after virologic outcome is determined. A prospective annual clinical note, any clinical evaluations (CT, ultrasound, EGD, MRI) and annual labs to observe persistence of HCV therapy response (HCV-RNA) & HCV co-morbid conditions (hematology, coags & serum chemistries) should be submitted. Co-morbid conditions, concomitant medications and health-related lab data will be collected from the submitted records and utilized to evaluate long term outcomes and disease progression. Participants who achieve SVR will be compared to participants who do not achieve SVR for the persistence of baseline co-morbidities and emergence of new co-morbidities post treatment. Participants who do not return to their local site for health care follow-up up to 3 years after HCV treatment baseline will be contacted by telephone to ascertain living status.

- Fibroscan, CT, ultrasound, MRI or other imaging at least once annually post viral outcome through approximately 3 years post treatment will be submitted according to the data milestone submission schedule
- Hepatology clinic notes at least once annually post viral outcome to through 3 years post treatment will be submitted according to the data milestone submission schedule. Complete blood cell count including platelets – at least once annually viral outcome through approximately 3 years post treatment will be submitted according to the data milestone submission schedule
- Measures of hepatic disease and function evaluation– at least once annually post viral outcome through approximately 3 years post treatment will be submitted according to the data milestone submission schedule
- Measures of renal disease and function – at least once annually post viral outcome through approximately 3 years post treatment will be submitted according to the data milestone submission schedule. Measures of other organ disease and function– done post treatment through 3 years post treatment will be submitted according to the data milestone submission schedule
- Prothrombin time/INR – at least once annually post viral outcome through approximately 3 years post treatment will be submitted according to the data milestone submission schedule. Additional lab reports documenting hepatic/organ insufficiency or failure OR other events of special interest may be requested from the site to fully characterize HCV treatment safety.
- Persistence of HCV RNA Virologic Outcome– HCVRNA collection completed after viral outcome is determined through 3 years post treatment will be submitted according to the data milestone submission schedule

7.5 Patient Reported Outcomes Data- Baseline, On Treatment, and Post-Treatment, and Long-Term Follow-up

The PRIORITIZE Study was developed to address outcomes of interest to patients and their caregivers. A 9-member HCV Patient Engagement Group (HCV-PEG) is acting as collaborators to this research and assisted in prioritizing HCV patients' informational needs ensuring harms or benefits to the patients are considered. Based on that input, the following patient reported outcomes surveys will be administered according to the Patient Reported Outcomes Schedule of Assessments (Table 5)

- HCV-PRO: The HCV-PRO is a newly developed survey designed to assess functional status of patients with HCV and measures physical, emotional and social functioning, productivity, intimacy, and perception of quality of life.
- PROMIS MEASURES- The HCV-PEG and researchers felt it would be useful to robustly and precisely measure six side effects reported by >10% of people in Phase III trials of the newly approved HCV therapies as well as common HCV systemic symptoms. The following five Patient-Reported Outcomes Measurement Information System® (PROMIS®) forms to obtain valid and precise measurement of specific, highly salient HCV systemic symptoms and/or treatment side effects: Fatigue, Cognitive Impairment, Sleep Disturbance, Diarrhea, Nausea, and Abdominal Pain. Each side effect/symptom is measured with a very brief form containing only 4-8 items from the larger item bank that were the best performing items in content validity and reliability. Change in PROMIS and HIT side effect scores from baseline to highest score during treatment will be evaluated.
- Headache Impact Test (HIT): Headaches were a common side effect noted in trials for both HARVONI® and Viekira Pak™(Phase I).
- Voils' Medication Adherence Survey that consists of 3 items assessing the *extent* of adherence to medications using a 5-point Likert scale ranging from "none of the time" to "every time".[37,38] These 3 items assess how often participants missed doses, skipped doses, or did not take doses over the past 7 days, and are combined into a single score shown to be reliable (a = 0.84).

Study participants will have the option of completing patient-reported surveys in person using standard paper versions (where necessary), via a web-based REDCap Patient Portal (link with instructions will be emailed to patient) or via phone interview. Patients completing web-based surveys respond via a secure URL from a home-based computer, and they decide whether they want to receive a call or email reminder prompting them to log into the URL and complete the survey. Data collected via REDCap Portals are transmitted to the HCV-TARGET Data Coordinating Center. Alternatively, if patients prefer, staff from our Survey Center (English and Spanish-speaking) will contact the patient at a previously approved phone number and convenient time to deliver the surveys via phone. Beyond convenience, phone interviews are critical to allow those with low literacy skills or without computer or access to participate in the study. All surveys (paper, electronic and telephone) will be offered in Spanish to sites with Spanish speaking populations. The PROMIS measures are already available in Spanish. We will undergo the proper techniques to translate the HCV-PRO, and Voils Medication Adherence into Spanish.

The telephone based surveys will be administered by The University of Florida Survey Research which has a state-of-the-art survey research program with a 93-station computerized lab operating seven days a week. Staff members conduct research on a variety of survey-related topics and conducts customized surveys and projects for UF research units and clinical trials. The center has the resources and training to complete the telephone surveys for this study with high attention to professionalism and sensitivities to patients needs during the survey process as well as in accordance with protections for privacy and protected health information.

7.5.a Future Biomedical Research

Samples collected for Future Biomedical Research are to be stored in appropriately consented participants.

In the event the subject does not consent to participate in Future Biomedical Research, any sample remaining after the collection for baseline RAP testing will be destroyed.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. The future research blood sample collected in the current trial may be used to study various causes for how participants may respond to a drug. The sample will initially be stored at the study central laboratory after collection.
Samples will be initially collected at sites' clinical/research laboratory or commercially available draw stations associated with the study central laboratory throughout the country and tested for baseline NS5a RAPs. The future research samples will remain at the study central laboratory until shipped for long-term storage at the University of Florida IRB approved Biorepository 'HCV-TARGET Biorepository Specimen Bank' for up to 15 years after the end of the study (database closure) at which time they will be destroyed. The sampling procedures, storage conditions and shipment instructions for participating sites will be provided in the supplemental laboratory manual.

Exploratory biomarker and virologic marker/resistance studies can be used for research purposes to identify potential biomarkers predictive of response to HCV treatment (in terms of mode of action, efficacy, dose, safety and tolerability), disease progression, to determine how best to monitor and treat HCV, development of a new medical product, or to explore complications of HCV disease and treatment. These studies will help to better understand the pathogenesis and treatment outcome of HCV infection through evaluation of biomarkers and virologic markers/resistance to predict disease outcomes and, possibly, response to antiviral therapy. In addition, genetic analyses may be performed on collected blood. The resulting pharmacogenetic information may improve treatment outcomes by stratifying patients who are more likely to respond to specific drug therapies, susceptible to developing adverse side effects and/or prone to more severe disease states.

Participants may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Participants may withdraw consent at any time by contacting the principal investigator at their local HCV treatment center (SITE). The site investigator will contact the University of Florida using the designated mailbox (PRIORITIZE@medicine.ufl.edu), and a form will be provided by the University of Florida to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the University of Florida to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

7.6 Progression of Liver Disease, Morbidity and Mortality Data

Clinical data used to evaluate progression of liver disease, morbidity and mortality will be abstracted from the medical records submitted according to the Schedule of Observations (Table 4). Comparison of regimens H, V and Z in terms of the risk of future clinical outcomes will rely on the application of machine learning algorithms to the patient's longitudinal follow-up data.[39] Using machine learning algorithms to predict outcomes (e.g., random forests with bagging) has been shown to outperform standard Cox regression approach because the machine learning approach can handle a large number of

predictor variables while coping with incomplete data. Incorporating longitudinal data into prediction models allows the predicted risk to be updated over time as additional evaluations accrue.[40] Predictions obtained before and after treatment can be used to characterize risk reduction and for a given treatment outcome. PRIORITIZE will use the following outcome measures: 1) Incident liver complications – hepatic decompensation (ascites, variceal bleeding, encephalopathy), cancer, liver-related death 2) Progression to cirrhosis – Increase in APRI to >2.0, Lok index to >0.5, or liver stiffness measurement to ≥12.0; 3) All-cause mortality and liver-related mortality; 4) Incident extra-hepatic manifestations of hepatitis C such as –diabetes mellitus, cryoglobulinemia with organ involvement and 5) Fibrosis progression/regression – change in FIB-4, APRI, and liver stiffness measurement over time. We anticipate that fibrosis will regress over time in patients who achieve SVR and that a decrease in fibrosis score will be observed in many patients with SVR by the end of the study. Passive follow-up 3 years after treatment will also include linking claims data to each patient on health service use, clinical diagnoses and procedure codes and through query of the National Death Index Plus. Various non-invasive methods for assessment of liver fibrosis and cirrhosis in patients with chronic hepatitis C have been validated.

We propose to apply both APRI and FIB-4 to all patients as these two indices comprise of routinely available labs that will be available longitudinally in hepatitis C patients. APRI and FIB-4 results will be used to determine baseline stage of liver disease and to determine progression or regression of liver disease after treatment. We will compare results based on APRI and FIB-4 and expect the conclusions regarding liver fibrosis progression and regression for each treatment arm will be similar. Both APRI and FIB-4 rely on two cutoff values, one for optimizing sensitivity and one for optimizing specificity (**Tables 4a and 4b**).[41,42] For example, low cutoff for assessing cirrhosis with APRI is <1.0 and high cutoff is >2.0. Summary sensitivity of APRI <1.0 in determining cirrhosis is 82% and summary specificity of APRI >2.0 is 92% in determining cirrhosis. Up to 40% of patients fall into the indeterminate zone, i.e. APRI between 1.0 and 2.0. Thus, it is recommended that more than one index based on blood tests or a sequential algorithm incorporating one index based on blood tests plus liver elastography be used to maximize the number of patients who can be classified. Although Fibroscan was approved by the US FDA in 2014, Fibroscan machines are not widely available outside major liver centers and even when available, liver elastography is not serially measured in most patients. We propose to apply both APRI and Fibroscan to assess baseline liver fibrosis in all patients in whom liver elastography is measured at baseline, and among this subset of patients who have follow up liver elastography measurement, we will again apply both APRI and Fibroscan to assess fibrosis progression or regression after treatment.

Table 6a Sensitivity and Specificity of APRI, FIB-4 and Fibroscan to Detect Liver Fibrosis Stage Metavir ≥F2

	Studies, n	Patients, n	Sensitivity, %	95% CI	Specificity, %	95% CI
APRI low	47	11696	82	77-86	57	49-65
APRI high	36	9602	39	32-47	92	89-94
FIB-4 low	11	2744	89	79-95	42	25-61
FIB-4 high	9	2115	59	43-73	74	56-87
Fibroscan	37	8346	79	74-84	83	77-88

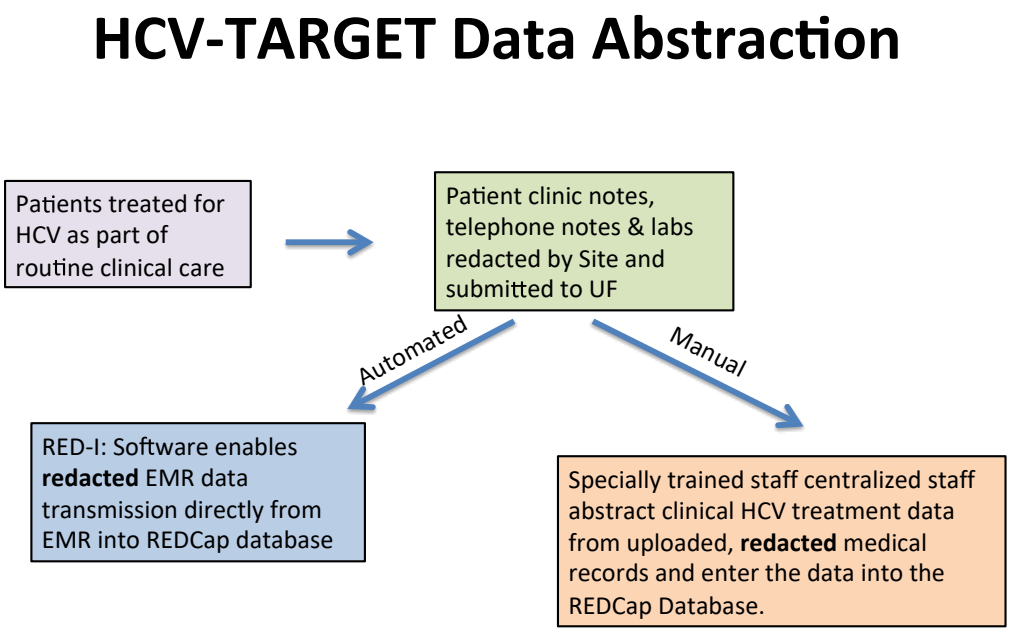
Table 6b Sensitivity and Specificity of APRI and Fibroscan to Detect Cirrhosis

	Studies, n	Patients, n	Sensitivity, %	95% CI	Specificity, %	95% CI
APRI low	24	7301	77	73-81	78	74-81
APRI high	19	6930	48	41-56	94	91-95
Fibroscan	36	7923	89	84-92	91	89-93

7.7 Procedures for Submitting Clinical Records for Study Observations

Several clinical and laboratory evaluations are routinely performed in the management of HCV treatment. These evaluations and clinical management are recorded as part of a patient's medical record. All clinic notes, nursing/staff telephone notes, evaluations and lab results collected to monitor the HCV baseline condition and treatment safety and efficacy are sources of data for PRIORITIZE. To collect HCV treatment and outcomes data, PRIORITIZE provides two pathways to submit safety and efficacy information from patient medical records recorded as part of standard clinical care.

1. Centralized Chart Data Abstraction Service (CDAS): Redacted medical records are uploaded into the study REDCap database for specially trained centralized teams of staff to manually abstract clinical, HCV treatment, safety and efficacy information as well as long term outcomes and disease progression into the study database (described in detail in Section 13.2).
2. REDCap Electronic Data Importer (RED-I): Redacted clinical data from the Electronic Medical Record (EMR) is electronically mapped and automatically uploaded into REDCap (described in detail in Section 13.3).



ALL available safety and efficacy data in the patient's redacted medical records will be recorded in the database, regardless of treatment regimen, dosing, or duration. Before submitting records for manual abstraction or through the automated RED-I platform, all elements of PHI defined by HIPAA *except dates of services* are redacted from laboratory test results, procedures, clinic/telephone notes and records related to adverse event and serious adverse event reporting. A study-coded identifier is added to the submitted records to help maintain subject confidentiality. HIPPA identifiers, the process of redacting records, and protection of patient confidentiality in PRIORITIZE is described in further detail in Sections 14.1 and

14.2.

8. ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. Adverse events reported in and abstracted from the submitted patient medical records (clinic notes, telephone notes, and labs) will be collected. Additionally, patient reported drug side effects will be collected through the study survey instruments. The patient reported drug side effects will not be coded for severity except where the survey instrument includes severity estimates directly from the patient report.

8.1 Adverse Event Intensity/Severity

For the purposes of the observational nature of the study clinical activities, adverse events identified by the chart data abstractors will be defined and coded centrally based on the following definitions:

- MILD: Adverse events and/or symptoms recorded in the medical record where no therapy was given to treat the event or where an over-the-counter medication/intervention ONLY was given to treat the event.
- MODERATE: Adverse events and/or symptoms recorded in the medical record requiring prescription medication treatment or any anti-HCV drug dose reduction
- SEVERE: Adverse events and/or symptoms requiring any anti-HCV drug discontinuation will be defined and coded as severe. ANEMIA events requiring blood transfusion will be coded as severe.

8.2 Adverse Event Relationship to HCV Treatment

For the purposes of this study, adverse event causal relationships will be captured as indicated on submitted medical records. Due to temporal associations during HCV treatment, adverse event causal relationships will be coded as "related" unless the event is clearly noted as "not related" to the HCV treatment regimen in the submitted records. For serious adverse events where the relationship cannot be adequately ascertained and for participants who discontinued treatment early due to an adverse event, the site PI or designee will be asked to assign relationship.

8.3 Abnormal Laboratory Evaluations

Any abnormal safety laboratory test assessment, obtained as part of the patient's standard of care, will be reported as an adverse event (AE) on the AE page of the eCRF ONLY if the laboratory abnormality meets one of the following criteria:

•Is considered to meet criteria as Serious
•Results in discontinuation from treatment (of any or all drugs)
•Results in dose adjustment of any anti-HCV medication
•Results in a requirement for new prescription medication

When applicable, a diagnosis term should be used to document an abnormal lab value or cluster of values.

8.4 Serious Adverse Events, Expectedness, and Causality of an Adverse Drug Reaction

8.4.1 Serious Adverse Event Definition

A *serious adverse event* (experience) or reaction is any untoward medical occurrence that at any dose of any of the HCV treatment medications:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,
- is medically important, or
- is a congenital anomaly/birth defect.

NOTE*:* The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.4.2 Expectedness and Causality

An *"unexpected" adverse event* is one, the nature or severity of which is not consistent with information in the applicable product information or package insert.

Causality assessment is required for clinical investigation cases; however, there is currently no standard international nomenclature. The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) to support a relationship to a drug/drug regimen.

8.4.3 *Expedited Adverse Event Reporting*

Expedited adverse event reporting will apply to events that meet serious criteria while on treatment in PRIORITIZE. **Any adverse event that meets the criteria for being serious, *regardless of expectedness or causality*, will be subject to *expedited* reporting as an adverse drug experience. Additionally, information that might materially influence the benefit-risk assessment of an approved medicinal product or that would be sufficient to consider changes in medicinal product administration should also be reported.**

8.4.3.1 Expedited Adverse Event Reporting Requirements

Adverse drug experiences meeting **expedited reporting criteria** specified above will be reported by submitting the VOLUNTARY Form FDA 3500 (MedWatch) when an event abstracted by the data abstraction staff at the University of Florida from the submitted medical record is noted to meet serious criteria. The data abstraction staff will complete the VOLUNTARY Form FDA 3500 with the data available in the clinical record and provide to the site PI to review for accuracy and to complete causality assessment. Every attempt will be made to submit these voluntary reports within 15 days of identification of the event. **The CCC will forward ALL VOLUNTARY MEDWATCH forms to the FDA regardless of SUSAR criteria.**

FDA Voluntary MedWatch Form:

https://www.fda.gov/safety/medwatch/howtoreport/downloadforms/default.htm

9. PREMATURE DISCONTINUATION

For participants who prematurely terminate HCV therapy, data will be used from the submitted medical records to assign the primary reason for early termination of treatment. There may be instances where information in the medical record does not sufficiently detail the reason for discontinuation. In those situations, the site PI will be asked to classify the reason for premature discontinuation and may use the following as a guide:

- Adverse event (specify)
- Virological failure (Meeting criteria for treatment futility as per drug label or local guidelines)
- Virological breakthrough
- Patient choice
- Non-adherence
- Administrative (Insurance changes)
- Lost-to-follow-up
- Other (specify)

For participants who die during the course of their HCV treatment, it will be the responsibility of the site PI to assign a cause of death based upon available clinical information, hospital records, and/or death certificate.

10. VIROLOGICAL RESPONSE DEFINITIONS

Non-responder: HCVRNA does not become undetectable and treatment is prematurely discontinued. Non-responder may be further characterized by the absolute change (log_{10}) in HCV RNA compared to baseline values

Sustained virological response (SVR): HCV RNA undetectable at least 12 weeks after therapy was discontinued

Relapser: HCV RNA was undetectable at the end of the course of treatment but became detectable at any time after discontinuing therapy

Treatment intolerant: These participants discontinued therapy prematurely due to adverse event or patient choice prior to completion of therapy. Duration of therapy and reason for discontinuation of any or all anti-HCV medications will be recorded. Post treatment virological response data will be provided where available in these participants to characterize SVR.

Virological breakthrough (VBT) during treatment

VBT will be defined as an increase of HCV RNA $\geq$ 1 log_{10} compared to nadir HCV RNA values during treatment. For participants with undetectable viral burden during treatment, an increase to > 100 IU/ml while still on treatment will define virological breakthrough.

11. PARTICIPANT WITHDRAWAL FROM PRIORITIZE

If a participant chooses to withdraw from observation in PRIORITIZE, all data collected up to the point of withdrawal will remain in the study database, but no further data may be collected. A request to

withdraw must be documented by the clinical center personnel. This is consistent with HIPAA guidelines and regulations.

12. STOPPING RULES/DATA AND SAFETY MONITORING PLAN

12.1 Data-Stream Monitoring

PRIORITIZE will be implemented using the fully functional HCV-TARGET infrastructure which comprises standardized, centralized chart data abstraction methods along with detailed data monitoring to increase the efficiency and quality of the database.

12.2 Interim Analysis of Safety Data

No interim analyses will be performed.

12.3 Stopping Rule

A formal rule for stopping the study will not be used.

13. STATISTICAL ANALYSIS STRATEGY

13.1 Overview

Best Practices: The statistical considerations and aim-specific analysis plans registered in this master protocol document were reviewed and updated in August 2017. To help ensure reproducible results, the *a priori* analysis plans specify detailed steps for the major estimators and inferential analyses along with guidelines for sensitivity analyses performed to assess the robustness of the major results to reasonable perturbations of the *a priori* assumptions, choices, and methods used. The plans also include a role for outcome-dependent exploratory analyses for hypothesis generation and necessary descriptive graphical and tabular methods used to characterize the participants, visualize the data and examine relationships among variables. Best practices for dealing with incomplete data will depend on the documented causes of missing, censored, and coarsened values. The main results will be obtained using appropriate model-based methods. To aid interpretation, simple means and proportions will also be tabulated. The outcomes of interest are binary (e.g. achievement of SVR), or interval-scale summary scores (e.g., PROMIS forms, HCV-PRO), or percent scores (e.g., adherence, persistence). Regardless of the scale of the outcome, the *strategy* for obtaining the main results is the same: for each regimen, and for the difference between regimens, point estimates of central tendency and variance will be obtained along with their 95% confidence intervals to indicate level of precision.

Primary Analyses. The main analyses will rely on intent-to-treat (ITT) estimation methods applied to those participants who started DAA drug therapy. The main analyses can thus be considered modified ITT analyses because (1) the analysis is conditional on the treatment to which the patient was randomized (even if the patient actually received a different treatment) and (2) participants who did not start treatment are excluded. Failure to start therapy after randomization is a particular kind of "drop out" and has many causes (e.g., death, change of employer/insurer, prior authorization (PA) filters, withdrawal of consent due to a burdensome PA application process). The baseline characteristics of randomized patients who did not start DAA therapy will play an important role in our investigation of the causes of not starting DAA therapy and our investigation of potential selection biases due to not starting DAA therapy.

Sensitivity Analyses. To guide our level of trust in the results from the main analyses, we will investigate the robustness of the study's main results to reasonable perturbations of the statistical methods and assumptions used. The domain of sensitivity analyses will include the following: use of "as-treated" estimation, use of "per-protocol" estimation, use of instrumental variable methods, use of other causal inference methods, examination of the influence of any extreme or questionable data values, examination of the impact of inclusion/exclusion of interaction terms in regression models, diagnostics for model goodness-of-fit, and descriptive analysis of model residuals. While there are always competing statistical methods and assumptions from which to choose, to help ensure reproducibility of research the main results should be obtained using a single choice of methods that is specified *a priori*; thus, uncertainty about the optimal choice of methods and assumptions is best handled by relegating competing approaches to an important role in the domain of sensitivity analyses. In this study, the application of ITT estimation methods to the participants who started DAA therapy is expected to be the most reasonable and advantageous strategy. All other methods and assumptions will play important roles in the domain of sensitivity analyses. For example, we anticipate a low frequency (1% to 2%) of "regimen switching" protocol departures (i.e., the patient withdraws consent and is treated with a different drug); consequently, induced bias is small and the mean-square error of the ITT estimator is very small compared to the large mean-square error of an instrumental-variable (IV) estimator that attempts to correct for the infrequent "regimen switching". (The instrumental variable would be the indicator of the regimen assigned by randomization.) Similarly, most of the mechanisms that cause drop-out prior to starting treatment are expected to be ignorable. For the few that may be non-ignorable (e.g., PA filters for Harvoni such as urine toxicology tests and denials due to minimal fibrosis scores), use of IV methods and other causal inference methods are not expected to be advantageous but will play a role in the sensitivity analyses to guide trust in the main results.

Available Data. About 1700 participants are expected to be consented to allow for approximately 1600 participants to randomized: 1600 = (725 to Z) + (724 to H) + (151 to V). Of those, about 1228 participants are expected to be randomized and successfully started on treatment: 1228 = (707 to Z) + (375 to H) + (146 to V). Recruitment data suggests that about 25% of those assigned to H, and 2% of those assigned to Z will fail to start treatment. Due to the discontinuation of assignments to regimen V (following the clinical practice shift away from regimen V, toward shorter therapies that pose less of a burden on patients), comparisons of regimen V to regimens H and Z will be based on data from the early participants who were enrolled while V was still available in the randomization process; that is, 146 participates who started treatment per each of regimens V, H and Z. In contrast, the primary analyses for comparing H and Z will be based on the data from all the subjects randomized to H or Z.

13.2 General Strategy and Heterogeneity of Treatment Effects (HTE)

Primary subgroups of interest are patients with 1) cirrhosis, 2) genotype 1a, and 3) Black American patients. The main analyses for the primary outcomes (e.g., SVR12 or side effect scores) will rely on statistical models conditional on carefully-defined covariates representing *cirrhosis*, *treatment naïve*, *genotype-1a*, *age-group*, *race*, *sex, treatment regimen* received, along with the interactions of *treatment regimen* with *cirrhosis status, genotype and race*. For specified outcome variables, the *baseline score* will also be included. The fitted model will provide parameter estimates that will be used to obtain point estimates, confidence intervals (CI) and hypothesis tests to (a) characterize and compare the three treatment regimens within subgroup, and (b) assess HTE represented by the treatment-by-subgroup interaction terms. The within-subgroup comparisons of pairs of regimens (H, Z, V) will include treatment equivalence tests and superiority tests. Secondarily we will generate new hypotheses by conducting exploratory HTE subgroup analyses for which we do not have a strong hypothesis about the directionality of effects. Point- and interval-estimates of treatment effects and differences will be obtained for

subgroups defined by age (>65 years, and <65 years), sex, presence of mental illness, and recent or active alcohol or illicit drug use.

For SVR12, we hypothesize that there is little or no HTE; in other words, we hypothesize that treatment-by-subgroup interactions are negligible. This means that regimens H, Z and V have similar cure rates in the subgroups of patients defined by cirrhosis, genotype 1a, and race. Within-subgroup differences in SVR between treatment arms are expected to be within the range of 0% to 6%. We also hypothesize that patients with cirrhosis, patients with genotype 1a, and Black American patients have lower SVR rates across the therapies (i.e., subgroup main-effects are substantial.) This expectation is based on previous uncontrolled trials and observational studies. For example, the review produced by ICER reported that among patients with cirrhosis, SVR was lower in patients treated with HARVONI® or Viekira Pak™, but only among the treatment naïve. The treatment-experienced patients with cirrhosis had similar response rates to treatment-experienced patients without cirrhosis, likely due to the longer treatment duration recommended for treatment-experienced patients with cirrhosis. The differences in response rate between the treatment arms {HARVONI® vs. Viekira Pak™ (Phase I)} were small regardless of cirrhosis or past-treatment status.

For Drug Side Effects, we hypothesize treatment differences as well as HTE related to cirrhosis; e.g., regimen V (with ribavirin) will yield higher frequency and severity of drug side effects, especially in patients with severe cirrhosis. We further hypothesize that medication non-adherence will be greater for regimen V than regimen H or Z due to drug side effects and daily pill burden.

13.3 Strategy for Aim 1 – SVR12

We conjecture that the three regimens are similar in the general target population and in subgroups and that the difference between any two regimens, $\Delta_{SVR} = (P_1\text{-}P_2)$ is in the interval (0%, 6%]. Based on input from our stakeholders, the regimens will be considered clinically equivalent if the difference in the SVR (Δ_{SVR}) is < 5%. The primary null hypothesis (H_o) to be tested is that the regimens are not equivalent in the general target population; i.e., that $|\Delta_{SVR}| \geq 5\%$. The alternative hypothesis (H_a) is that the regimens are equivalent; i.e., that $|\Delta_{SVR}| < 5\%$. Complementary to this test procedure, a "superiority" test of the null hypothesis that $\Delta_{SVR} = 0$ will also be performed. It is easily possible to arrive at a conclusion such as $0\% < \Delta_{SVR}$ and $|\Delta_{SVR}| < 5\%$; i.e., we establish that one regimen is superior but it does not matter because the difference is not clinically important. To provide future patients with personalized information, i.e. "what is the SVR for a patient like me", the model will be used to tabulate profile-specific point- and interval-estimates of the probability of SVR12.

13.4 Strategy for Aim 2 – Drug Side Effects

Because patients have pre-existing symptoms at baseline that are similar to known drug side effects (e.g., fatigue), for each *PROMIS* score of interest we will condition on the baseline value of the *PROMIS* score as a covariate, and analyze change from baseline to the highest (worst) score during treatment. Additional supportive tabulations for each of the 32 side effects will be explored; e.g., the incidence of new side effects and the exacerbation of existing symptoms during treatment will be characterized in regard to raw frequency, severity and distress score. Linear model methods will be applied (see general strategy and HTE above). For each comparison of interest a multiple-comparisons procedure will provide an overall multivariate test (across PROMIS measures) and a set of component univariate tests. Drug side effects data will be collected from medical records to enrich patient's survey data and provide a complete record of patient-reported, physician documented, and lab defined drug side effects.

13.5 Strategy for Aim 3 – Adherence and Persistence

Based on the patient-reported Voils' Medication Adherence Survey, each participant's level of *adherence* will be classified as high or low for purposes of the analysis of treatment effects. We anticipate that 50% to 95% of participants will achieve the high level of adherence, depending on regimen and patient

characteristics. Non-adherence is expected to be greatest for regimen B due to drug side effects and daily pill burden. Analysis will rely on logistic regression methods. Similarly, a generalized regression model for *persistence* will provide point and interval estimates and test procedures as described above (general strategy and HTE).

13.6 Strategy for Aim 4 – Change in Systemic Symptoms

Six PROMIS® scores recorded at baseline and at one and three years after treatment will be used to evaluate change from baseline. Linear model methods for response will be applied (see general strategy and HTE) and modified to account for baseline scores and response to treatment (SVR). The analysis will focus on point- and interval-estimates of the magnitude of treatment effects. For each comparison of interest a multiple-comparisons procedure will provide an overall multivariate test (for PROMIS measures) and a set of component univariate tests. Sensitivity analyses will include use of modified and alternative assumptions and methods. For example, for any PROMIS score with heavily skewed and/or bimodal distributions we may examine the impact of using alternative modeling assumptions (e.g., a zero-inflated log-normal model).

13.7 Strategy for Aim 5 – Progression of Liver Disease

In terms of the risk of long-term progression/regression of liver disease, characterization and comparison of the regimens will rely on the application of machine learning algorithms to the patient's longitudinal follow-up data. Rather than relying on actual occurrence of long-term clinical outcomes, which is hindered by the relatively short time frame, we will apply validated prediction models to estimate the risk of clinical outcomes for each regimen in patients who achieved SVR versus those who did not.[43] These longitudinal models will rely on baseline demographic variables and on 3 years of follow-up evaluations of BMI, labs (CBC, liver panel, INR, Cr), imaging (US/CT/MRI), liver stiffness measurement by Fibroscan, and histology. These prediction models for risk of liver outcomes will be re-fitted annually as follow-up data accrues. The regimens will be compared in terms of the changes in predicted risks of liver outcomes over time. For the primary outcome of fibrosis regression, we will compare treatment groups as follows: (1) % with fibrosis regression at up to 3 years post treatment baseline, (2) % with net fibrosis regression at up to 3 years post treatment baseline (% with fibrosis progression will be subtracted to obtain net improvement), and (3) % predicted to have fibrosis regression up to 3 years post treatment baseline.

13.8 Strategy for Aim 6 – Persistence of Viral Cure or Re-infection

Follow-up at 3 years will be used to characterize and compare the treatment regimens overall and in subgroups in terms of recurrence of infection in those participants who had achieved SVR. The analysis will focus on point- and interval-estimates of rates.

13.9 Strategy for Aim 7 – Functional Status

The HCV-PRO score recorded at baseline and at one and two years after treatment will be used to evaluate change from baseline. Linear model methods will be applied (see general strategy and HTE) and modified to account for baseline score and response to treatment (SVR). The analysis will focus on point- and interval-estimates of the magnitude of treatment effects together with treatment equivalence tests and superiority tests.

13.10 Strategy for a New Aim – Impacts of Mandated Prior Authorization

Data from the recruitment and randomization process will yield a secondary publication investigating the negative impact of payor-mandated prior authorizations on treatment start rates. Prior to any examination of data concerning the impact on clinical and PRO outcomes, a detailed

statistical analysis plan will be developed for this additional investigation. The publication will emphasize that this additional investigation was not envisioned in the original *a priori* analysis plans.

13.11 Use of Causal Inference Methods

Causal inference methods will play important roles in (1) sensitivity analyses which use reasonable perturbation of methods and assumptions to guide trust in the main results, and in (2) any comparisons of the PRIORITIZE data to other databases such as that of the TARGET Study.

Sensitivity Analyses. For example, sensitivity analyses using randomization as an instrumental variable will be useful in regard to guiding our level of trust in the results of tests of equivalence of regimens on SVR rates. For SVR, instrumental variable methods will include two-stage logistic regression (2SLR), two-stage residual inclusion (2SRI), and bivariate-probit estimation. In all of these, the randomized treatment assignment will be the instrumental variable. More generally, the sensitivity analyses may include two-stage least squares (2SLS) IV methods and other causal inference methods such as inverse probability of treatment weighting (IPTW) based on propensity scores. These methods are not expected to advantageously improve estimation and inference.

Study Comparisons. For any comparisons (if any) of the PRIORITIZE data to other databases (e.g., HCV-TARGET) a broad variety of causal inference methods would be used: e.g., covariate-balancing propensity score methods, partitioning the covariate space for purposes of stratum-specific covariate matching, inverse probability weighting (IPW), and doubly robust methods.[44,45,46,47,48] These methods are more computationally intensive and require careful use of diagnostic methods (e.g., for covariate balance) and an extensive set of sensitivity analyses. It should be noted that the required assumption of "no unmeasured confounders" would be unverifiable. Although limited by the necessity of making additional assumptions and conjectures, efforts would be made to investigate the potential magnitude of residual bias that would exist if any unmeasured confounders exist. Use of propensity-score methods would rely on an extensive set of covariates measured at baseline. For purposes of estimation of a propensity score model, missing covariate values will be addressed via multiple imputations and the resulting multiplicity of propensity scores would be averaged together as proposed by Mitra and Reiter.[49]

13.12 Methods for Coping with Missing Data

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 and clinical data even when the participant terminates treatment earlier than scheduled. Depending on the mechanisms which cause loss-to-follow-up for outcomes such as the PROMIS Scores at 1 year, multiple imputation methods may be appropriate. Competing model-based methods will be examined for purposes of sensitivity analysis.

13.13 Sample Size Rationale

In total, we anticipate that about N = 1700 participants will be consented and enrolled, with at least 1228 being both successfully randomized and successfully starting treatment as follows: 1228 = (707 to Z) + (375 to H) + (146 to V). Due to the discontinuation of assignments to regimen V, only 154 enrollees were assigned to regimen V. Of those, only 146 started V regimen treatment. While equal numbers of participants are assigned by randomization to H and Z, the sample size expectations take into account the higher rate of failure to start treatment that is inherent for those assigned to regimen H.

About 15% of participants in each treatment arm will be classified as cirrhotic. The rationale for that original target was based in part on an assumption that 50% of the participants would have cirrhosis and

that outcomes would depend heavily on the presence or absence of cirrhosis. The originally envisioned target sample size was 625 participants per cirrhosis subgroup per regimen (H, Z, V): $625 \times 2 \times 3 = 3750$ total. It was assumed that cirrhotic and non-cirrhotic patients would have substantially different severity of disease and substantially different clinical experiences in terms of SVR and PROs. In order to address the assumed existence of those strong "cirrhosis main effects", it was assumed that a substantial sample size would be needed per stratum (cirrhotics, non-cirrhotics) per regimen (H, Z, V).

Based on recent information, we anticipate that ~ 15% of the PRIORITIZE participates will be classified as cirrhotic and most of those cirrhotic participants will have be in milder stages of liver disease (e.g., MELD scores < 10). We therefore anticipate that the estimates and inferences for the overall combined target population will be the most important results. Estimates and inferences for the cirrhotic sub-population (or the smaller sub-population of decompensated cirrhotic patients) will necessarily be based on samples sizes smaller than about 87 - 116 participants (or about 10 - 20 decompensated cirrhotic participants) in each of the H and Z treatment arms. We anticipate that only about 23 of the 146 participants receiving regimen V will be classified as cirrhotic.

The current target sample sizes reflect the scarcity of cirrhotic patients and discontinuation of regimen V, as well as expectations about rate of recruitment, rates of successful randomization and treatment starts, and the length of time available to conduct the study. While the target sample sizes have been updated, the statistical analysis plans have not been changed by the sample-size considerations. Rather, some of the anticipated results have risen in importance: the estimates and inferences for the overall combined target population (especially for H and V) will be the most important results, while estimates and inferences about sub-populations defined by cirrhotic status necessarily will be less important than was anticipated in 2014 when PRIORITIZE was initially envisioned.

The performance characteristics of the target sample sizes were evaluated in terms of the anticipated levels of power for the proposed hypothesis tests and anticipated levels of precision for important statistical estimators.

General Assumptions Underlying the Sample Size Analysis.

The main analysis will focus on point and interval estimates of treatment effects and difference. Inferences will rely on two kinds of tests: a 2-sided superiority test of size α of the null hypothesis H_o: "the difference is exactly zero", and an equivalence test of size α of H_o: "magnitude of difference exceeds a clinically important threshold." Equivalence test power levels are highest when regimens are identical in their effect. Primary consideration was given to the analyses for regimens H and Z.

Table 7. Target Numbers of Patients Successfully Started on Treatment

Original Target Sample Sizes				Updated Assumptions and Target Sample Sizes					
	Cirrhosis[1]					Cirrhosis[2]			
	No	Yes	Total	Randomized		No	Yes	Total	PRO[5]
H	625	625	1250	~ 723	**H**	320	55	375[4]	300
Z	625	625	1250	~ 723	**Z**	600	107	707	566
V	625	625	1250	154	**V[3]**	122	23	146	117
			3750					1228	982
Assumptions					Assumptions				

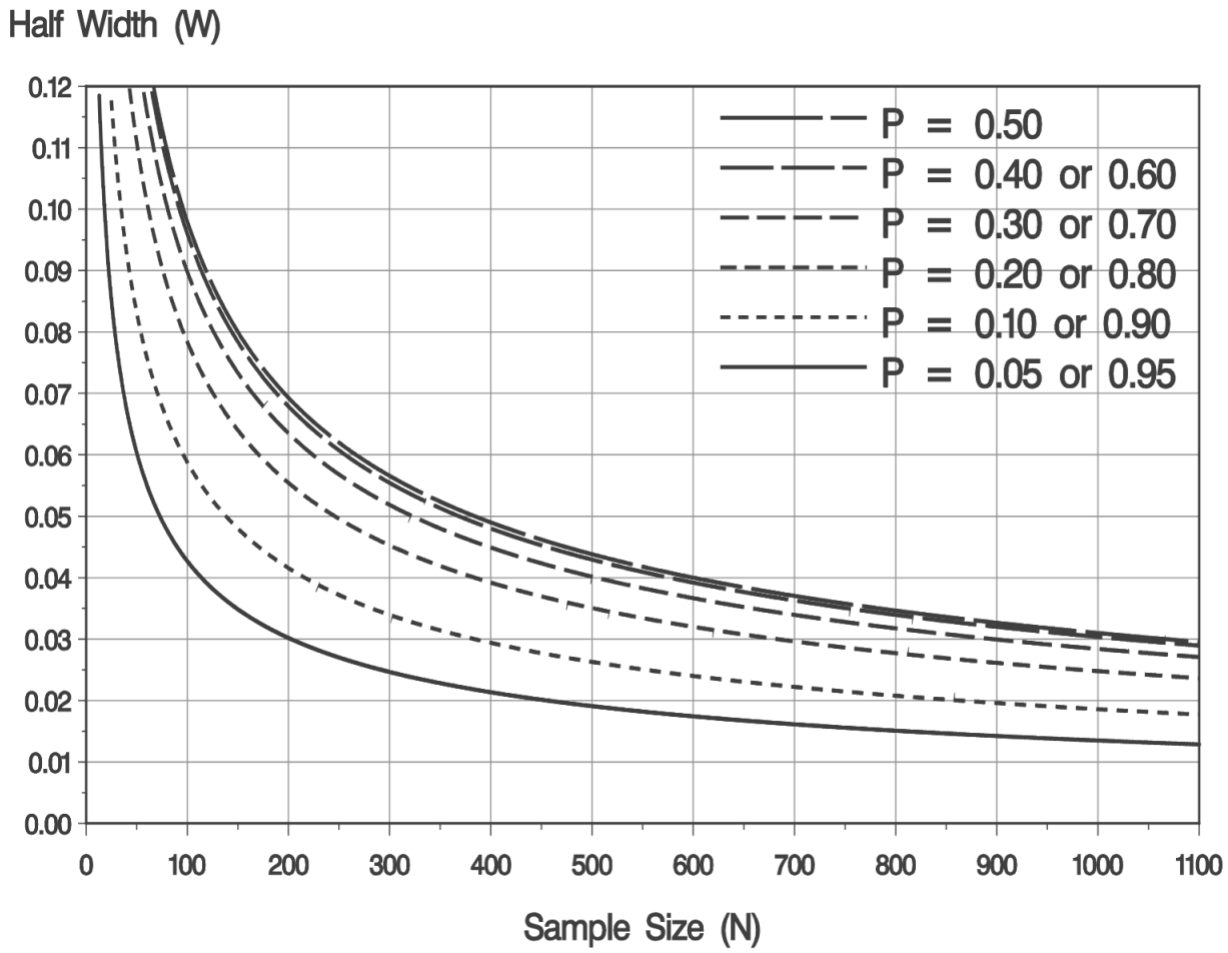
[1] 50% will have cirrhosis		[2] Only 15% will have cirrhosis
		[3] Regimen **V** was discontinued
		[4] Rates of treatment starts for **H**
		[5] 80% will have complete PRO data

Power curves and precision curves were analyzed assuming that only 15% of participants in each treatment cohort will have cirrhosis and that most of the cirrhotic patients will be in milder stages (e.g., MELD < 10). The sample size available to each estimator and to each test procedure will vary. For purposes of sample size analysis, the power curves are based on the assumption that the test in question will be based on a unified model for the data –which is the proposed approach in the data analysis plan. For purposes of computation of these curves, we assume balance of covariates, inclusion of the baseline score in models for change from baseline, and that the tests are those of size = $\alpha = 0.05$.

We assume that 80% of the subjects will have complete PRO data, while about 100% of the subjects will have sufficiently complete SVR data.

SVR - Anticipated Precision

What is the anticipated width of the confidence interval for an SVR rate? The figure below addresses this question about the anticipated precision for SVR estimates (and other rates and proportions.) For binary outcomes such as SVR (yes, no), or *medication adherence* (high, low), the primary analyses will provide statistical estimates of the population rate (P). The anticipated level of precision for the estimated proportion can be obtained from the figure. For example, if n = 700 and $P = 0.95$ is the observed point-estimate, then half the width of a symmetric approximate 95% confidence interval (CI) is W = 0.016 and thus an approximate 95% CI would be 0.950 ± 0.016 or [0.934, 0.966].

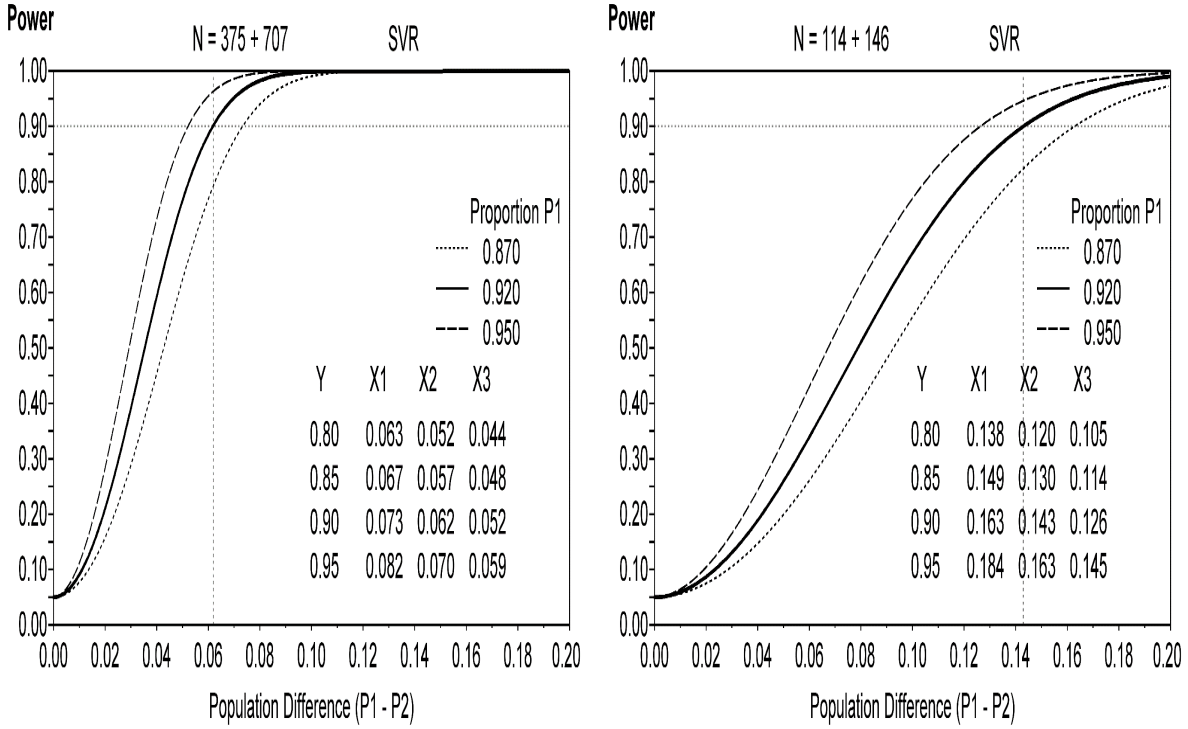

Half Width (W)
0.12
0.11
0.10
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.00
0
100
200
300
400
500
600
700
800
900
1000
1100
Sample Size (N)
P = 0.50
P = 0.40 or 0.60
P = 0.30 or 0.70
P = 0.20 or 0.80
P = 0.10 or 0.90
P = 0.05 or 0.95

SVR – Anticipated Power Curves for the Superiority Test:

The null hypothesis is H_o "$P_1 = P_2$" in which P_1 and P_2 are the regimen-specific SVR rates in the target population. The null hypothesis is a statement about the population from which the sample is drawn. Based on knowledge from previous studies, it is reasonable to conjecture that $(P_1 - P_2)$ may have a value in the interval [0.00, 0.06]. The anticipated levels of power for the tests are summarized under the assumption that $P_1 > P_2$ for conjectured values of P_1 and a range of values of $(P_1 - P_2)$ in the figures below.

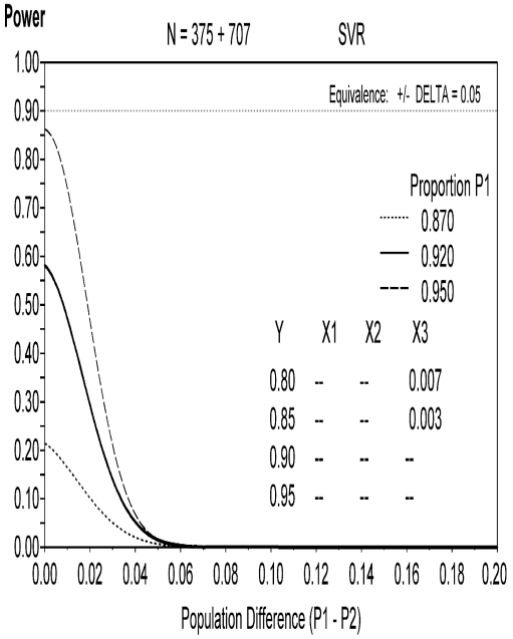
The figure labeled "N = 375 + 707" refers to comparison of regimen H to regimen Z.
Reading from the curve, if $P_1 = 0.92$ and $(P_1 - P_2) \geq 0.062$, then we could anticipate a 90% chance of drawing a sample of participants from the target population such that the test turns out to be statistically significant. This also means there would be a 10% chance of not rejecting the null hypothesis. Or if $P_1 = 0.92$ and $(P_1 - P_2) = 0.035$, then we could anticipate a 50% chance rejecting the null hypothesis, H_o "$P_1 = P_2$". If the null hypothesis is true, then there is a 5% chance of rejecting H_o, and this is true for all choices of sample size.

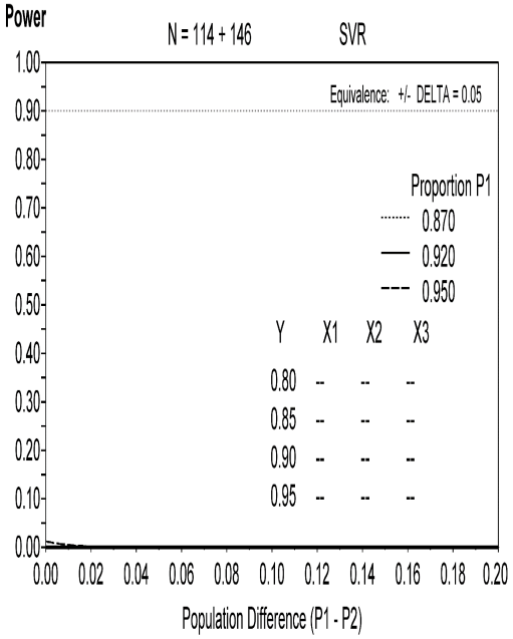
The figure labeled "N =114 + 146" refers to comparison of regimen V to regimen H.
If for example $P_1 = 0.92$, the curve indicates there would be a 90% chance of rejecting the null hypothesis only if $(P_1 - P_2) \geq 0.143$ in the target population --which means $P_2 \leq 0.78$ while $P_1 = 0.92$.

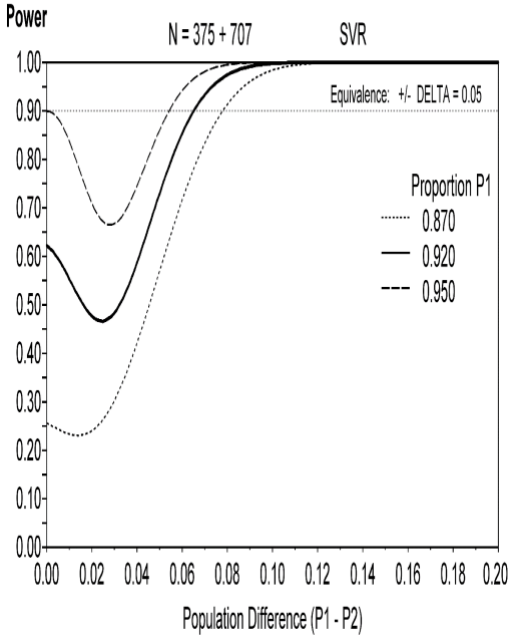


SVR – Anticipated Power Curves for the Equivalence Test:

The probability of rejecting the null hypothesis, "not equivalent", is summarized in the figures below. Power levels are highest for cases in which the two regimens are identical in terms of the population rate; that is, $(P_1 - P_2) = 0$ in the target population. The power level decreases rapidly as the magnitude of difference, $|P_1 - P_2|$, increases. In the figures, it is assumed that P_1 is the larger rate and P_2 is the smaller rate. For "N = 375 + 707", larger SVR rates are more favorable and power is anticipated to be near 80% when (P_1-P_2) is close to zero.
For "N = 114+146" the curves are flat near 0.00; i.e., that test almost surely will be inconclusive.







SVR – Chances that at least one of the two tests is statistically significant

There can be a substantial probability that at least one of the two tests (equivalence, superiority) will be statistically significant. The likelihood of that is a function of the values of P_1 and (P_1 - P_2) in the target population as illustrated in the following figure. The vertical axis is the probability that a sample of participants will be recruited such that it turns out that at least one of the two tests happens to be statistically significant.

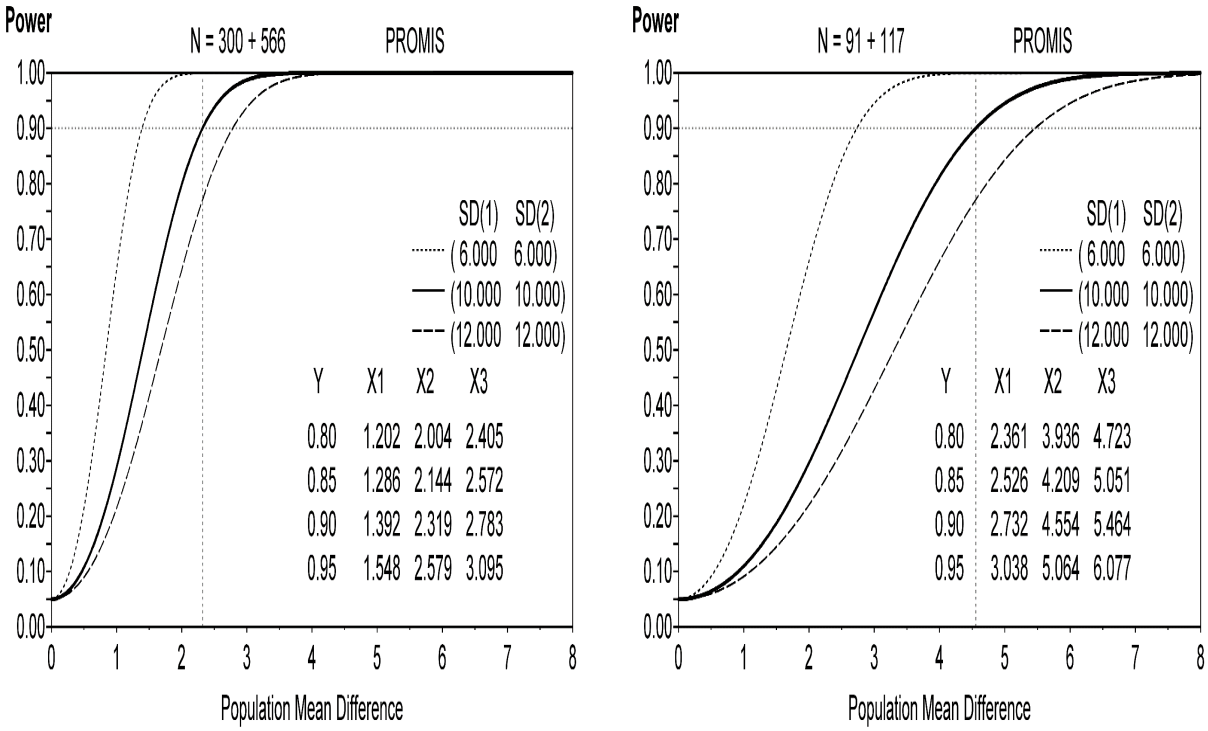
(Note: In these figures, each point on each curve was obtained by simulating the study 1,000,000 times using a test procedure which relied on a continuity-corrected Wald confidence interval.)

PROMIS Scores – Anticipated Power Curves for the Superiority Test

The standardized T-scores have exhibited standard deviations (SD) ranging from 6 to 12 at baseline in previous studies of 32 HCV patients (Evon, data unpublished). The CID ranges from 3 to 6. Separate tests will be performed for each of the six T-scores.

In the comparison of regimens H and Z ("N = 300 + 566"), anticipated power of the superiority test would be 90%, for example, if the population standard deviation is 10.0 (for both regimens) and the population mean difference is at least 2.319.

Again, under the conjecture that the population standard deviation is 10.0 (for both regimens), for the H-vs-V comparison ("N = 91 + 117") the anticipated power of the superiority test exceeds 90% only when the population mean difference is at least 4.554.



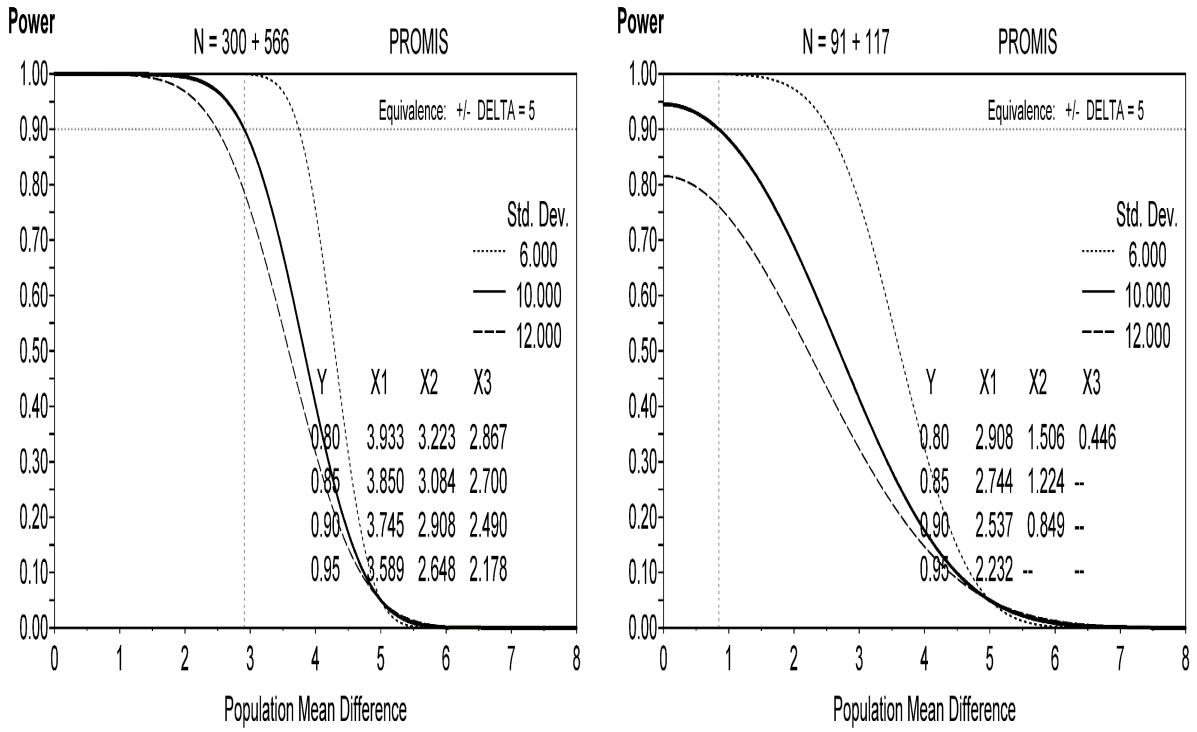
PROMIS Scores – Anticipated Power Curves for the Equivalence Test

The standardized T-scores have exhibited standard deviations (SD) ranging from 6 to 12 at baseline in previous studies of 32 HCV patients (Evon, data unpublished).

The probability of rejecting the null hypothesis, "not equivalent", is summarized in the figures below. Power levels are highest for cases in which the two regimens are identical in terms of the mean difference in the target population. The power level decreases rapidly as the magnitude of difference increases.

In the comparison of regimens H and Z ("N = 300 + 566"), anticipated power of the equivalence test would be 90%, for example, if the population standard deviation is 10.0 and the population mean difference is less than 2.908.

Again, under the conjecture that the population standard deviation is 10.0, for the H-vs-V comparison ("N = 91 + 117") the anticipated power of the equivalence test exceeds 90% only when the population mean difference is less than 0.849.



As discussed below, for the H - vs. - Z comparison ("N = 300 + 566"), it is likely that at least one of the two test procedures (equivalence, superiority) will be statistically significant.

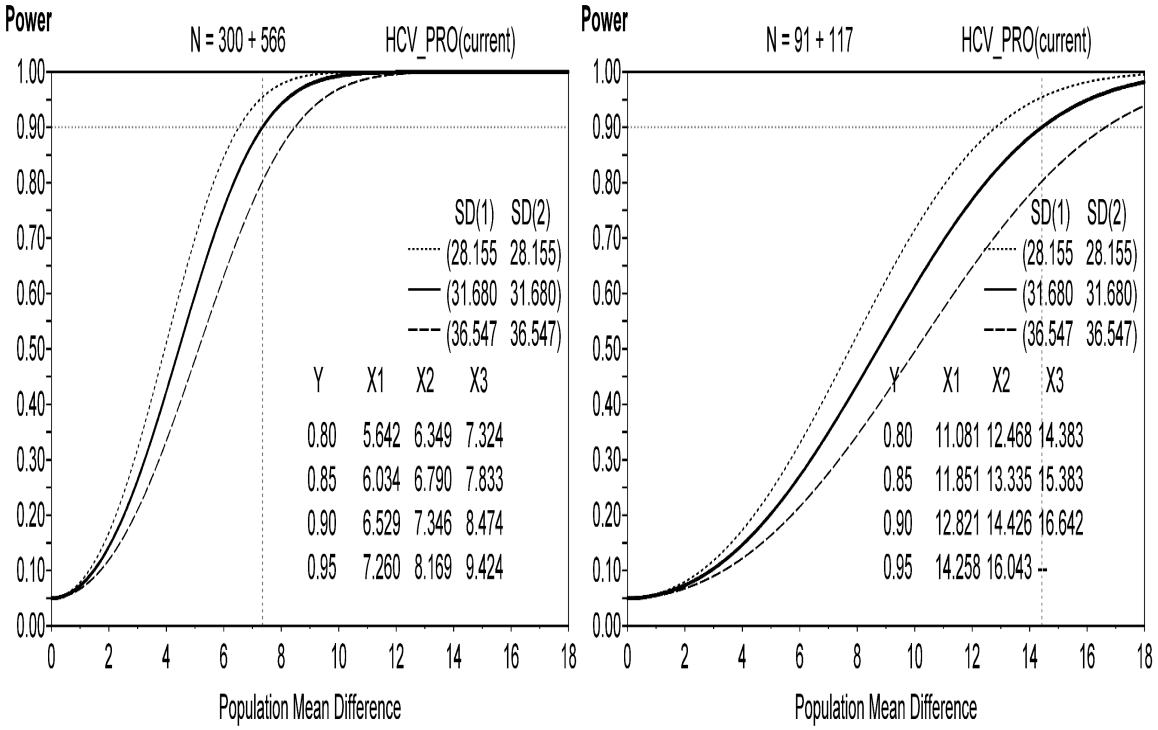
HCV-PRO – Anticipated Power Curves for the Superiority Test

The scale ranges from 0 to 100. A reduction of 10 or more points was considered clinically significant by Anderson, et al., (2013), with the estimates shown in the table.

Treatment status	*N*	Mean	SD	Min	Max
Previously treated	86	56.92	25.92	7.813	100.0
Currently treated	51	39.06	31.68	0	98.44
Never treated	104	65.61	22.25	4.688	100.0

In the comparison of regimens H and Z ("N = 300 + 566"), anticipated power of the superiority test would be 90%, for example, if the population standard deviation is 31.68 (for both regimens) and the population mean difference is at least 7.346.

Again, under the conjecture that the population standard deviation is 31.68 (for both regimens), in the H-vs-V comparison ("N = 91 + 117") the anticipated power of the superiority test procedure would be 90% on if the population mean difference is at least 14.426.



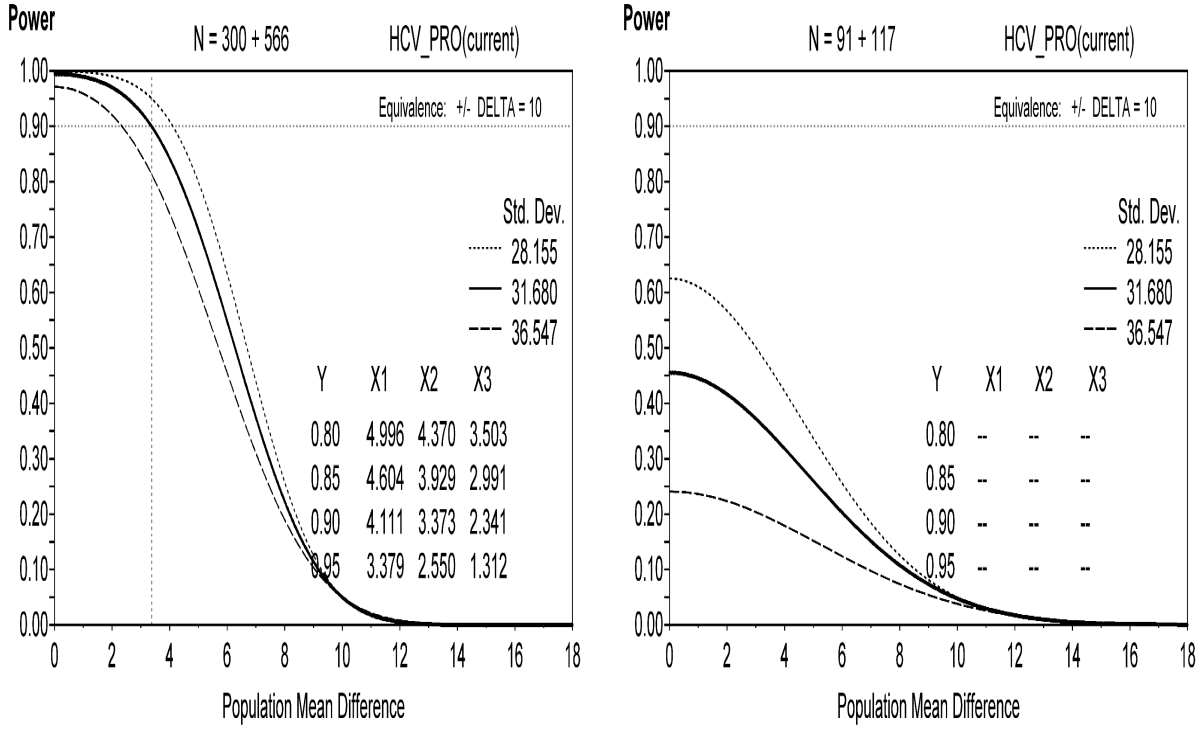
HCV-PRO – Anticipated Power Curves for the Equivalence Test

The scale ranges from 0 to 100. A reduction of 10 or more points was considered clinically significant by Anderson, et al., (2013), with estimates shown in the table.

The probability of rejecting the null hypothesis, "not equivalent", is summarized in the figures below. Power levels are highest for cases in which the two regimens are identical in terms of the mean difference in the target population. The power level decreases as the magnitude of difference increases.

In the comparison of regimens H and Z ("N = 300 + 566"), anticipated power of the equivalence test would be 90%, for example, if the population standard deviation is 31.68 and the population mean difference is less than 3.373.

Again, under the conjecture that the population standard deviation is 31.68, in the H-vs-V comparison ("N = 91 + 117") the equivalence test is more likely to be inconclusive.



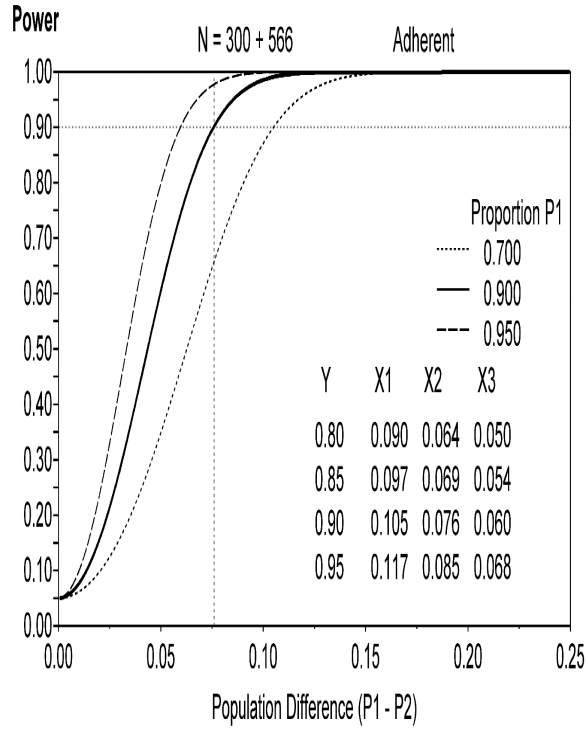
For the H-vs.-Z comparison ("N = 300 + 566"), it is likely that at least one of the two test procedures (equivalence, superiority) will be statistically significant.

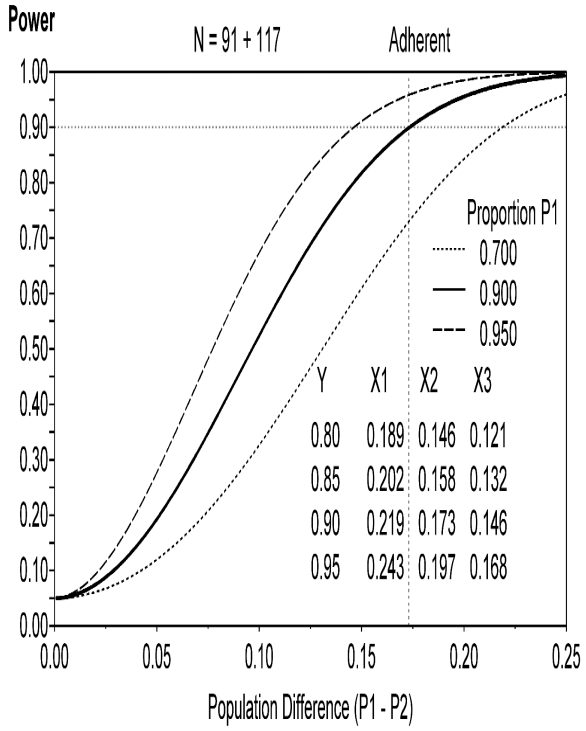
Medication Adherence – Anticipated Power Curves for the Superiority Test

Based on patient-reported Voils' Medication Adherence Surveys, each participant's level of adherence will be classified as "high" or "low". We anticipate that P = 70% to 95% of participants will achieve the "high" level of adherence; that is, P_1 has a value between 0.70 and 0.95.

In the comparison of regimens H and Z ("N = 300 + 566"), anticipated power of the superiority test would be 90%, for example, if $P_1 = 0.90$ and $(P_1-P_2) \geq 0.076$ --which means $P_2 \leq 0.824$.

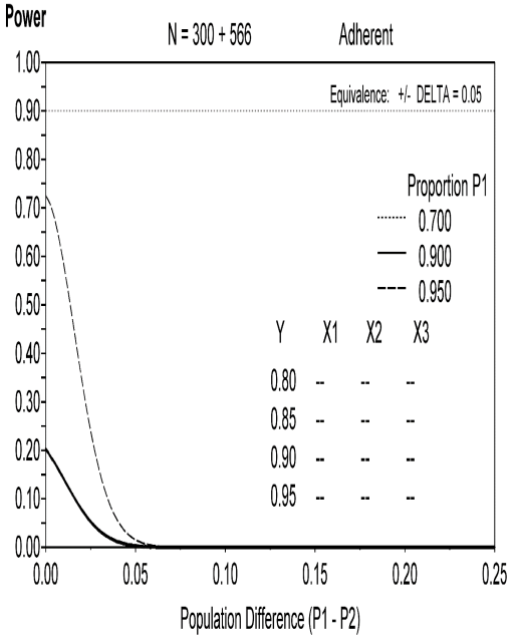
In the comparison of regimens H and V ("N = 91 + 117"), anticipated power of the superiority test would be 90%, for example, if $P_1 = 0.90$ and $(P_1-P_2) \geq 0.173$ --which means $P_2 \leq 0.727$.

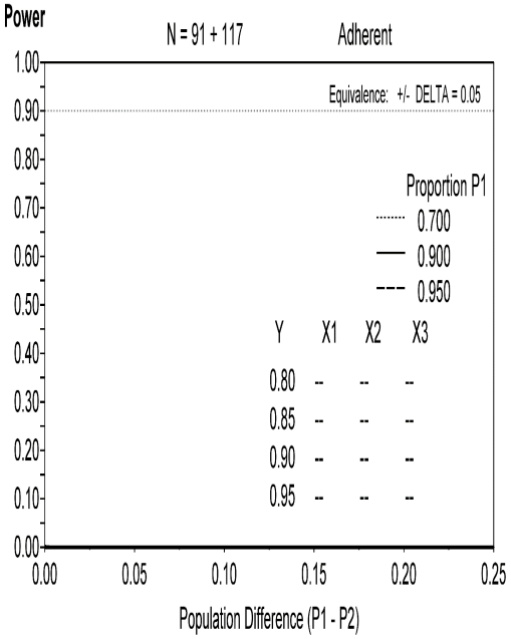


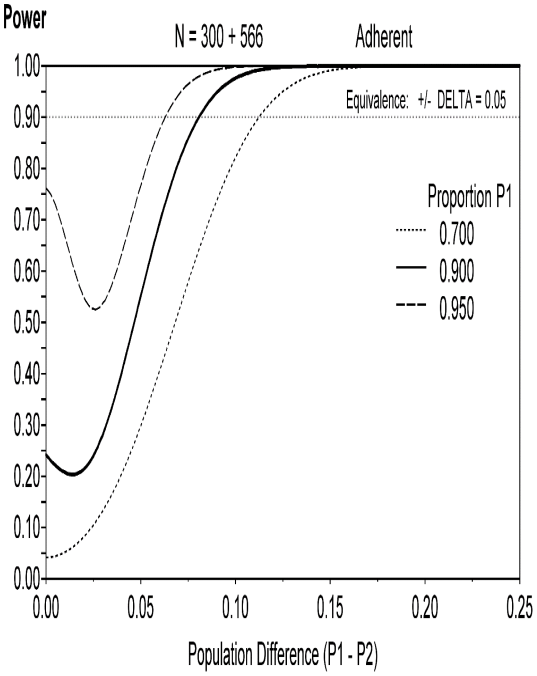


Medication Adherence – Anticipated Power Curves for the Equivalence Test

Based on patient-reported Voils' Medication Adherence Surveys, each participant's level of adherence will be classified as "high" or "low". We anticipate that P = 70% to 95% of participants will achieve the "high" level of adherence; that is, P_1 has a value between 0.70 and 0.95. In the comparison of regimens H and Z ("N = 300 + 566") the equivalence test is likely to be inconclusive. For H-vs.-V "N = 91 + 117", the equivalence test is almost sure to be inconclusive.







Adherence – Chances that at least one of the two tests is statistically significant

There can be a substantial probability that at least one of the two tests (superiority, equivalence) will be statistically significant. The likelihood of that is a function of the values of P_1 and (P_1 - P_2) in the target population --as illustrated in the figure at left.

The label "N = 300 + 566" refers to the sample sizes for regimens H and Z. The vertical axis is the probability that a sample of participants will be recruited such that it turns out that at least one of the two tests happens to be statistically significant. There is a small chance that both tests (superiority test, equivalence test) will happen to be statistically significant.

14. DATA MANAGEMENT

14.1 Overview

HCV-TARGET will establish standardized systems and operational protocols to ensure data quality control, security, and compliance with all applicable standards.

Data Quality and Integrity is a central requirement of research. Data collection and data entry in multi-center studies can be very complex, with high variability amongst centers[50],[51],[52]. In multi-center, practice-based studies, high rates of errors and inconsistencies have been observed with abstraction of protocol defined data points, lack of protocol defined data contained within the medical record, incorrect transcription of data from a medical record, and variability of conventions used to standardize data entry [39]. Studies of practice-based research have shown benefits to utilizing a central data management center to ensure data quality and consistency and reduce these types of errors [38].

14.2 Centralized Chart Data Abstraction

In order to reduce chart data abstraction errors and inconsistencies and improve data quality, PRIORITIZE will utilize a specially trained Centralized Chart Data Abstraction Service team at the CCC/respective country Abstraction Core (CDAS) as the method for chart abstraction. Participating sites will provide copies of clinically available medical record source data on enrolled participants to the CDAS. This data includes clinic notes, nursing/staff telephone notes, evaluations and lab results generated in standard care to monitor the HCV baseline condition, on-treatment safety and efficacy as well as long-term health outcomes. The CDAS will abstract and enter the data from those provided participant medical records into the database.

14.3 REDCap Electronic Data Importer (RED-I)

In addition to CDAS to submit health records data, the University of Florida CTS-IT team built RED-I to securely obtain redacted data directly from the electronic health record (EMR) and push it into REDCap in an automated fashion. A site level patient index with the patient identifiers mapped to HCVT Target Subject Numbers is maintained at the site and used by the site level EMR data teams so patient EMR data is accessed without sharing the identifiers centrally to the RED-I software maintainers. The PHI *with the exception of dates of service* is removed from the EMR data and replaced with the subject's PRIORITIZE identifier before pushing it over an encrypted pathway into the study REDCap database. The UF CTS-IT team will work directly with each respective site's IT and/or EMR team to establish and maintain the software and data feed along with quality checks to ensure secure processes. Where RED-I software is established at the site, electronically mapped data will be submitted in conjunction with CDAS.

14.4 Submitting Records for Abstraction

Before submitting records for abstraction, site staff will redact all elements of PHI (see section 14.2) defined by HIPAA *except dates of services* on all laboratory tests, procedures, clinic/telephone notes and records related to adverse event and serious adverse event reporting. Sites will add a study-coded identifier to the submitted records to help maintain subject confidentiality. Patient identifiers such as patient name, full date of birth, address, etc. can be viewed by the DCC or CCC to facilitate onsite and remote monitoring of the data and compliance with the protocol, however, with the exception of dates, PHI identifiers will not be included on any datasets used for the overall safety and efficacy database and analyses, making the clinical database a *limited data set*. In instances where a PHI identifier other than a date of service is present on a redacted record received for CDAS, delegated CDAS personnel will redact that information.

To ensure security with transmitting the records, sites will upload the redacted medical records into the Data Management System. Chart Data Abstractors will access the redacted records from this system to abstract the protocol-defined data into the study database. Those records will be maintained by CDAS staff to facilitate data monitoring as needed.

14.5 The Data Coordinating Center (DCC) & Data Management System

The DCC resides in the School of Medicine, College of Gastrointestinal and Biological Disease (CGIBD) at UNC-Chapel Hill, CGIBD provides the systems and associated support resources to enable efficient professional collection and management of research data. The web-based Research Electronic Data Capture (REDCap) database software is the proposed Data Management System.

REDCap has been used in over 248,000 projects with over 340,000 end users in 99 countries. REDCap is a mature, robust system designed expressly for the purpose of interactive web-based recording of research data.

All data will be collected, processed, transmitted and stored via REDCap. This system will be housed on a computing infrastructure that enables compliance with FDA 21 CFR Part 11, HIPAA, HITECH, and other applicable standards pertaining to the security of sensitive data (PHI) at rest and in transit. Should compliance with additional standards become necessary in the future, our selection of hosting provider will make possible the adoption of such standards.

The DCC personnel also provide programming and validation for data quality assurance processes, scheduled and ad-hoc progress reports, medical coding of research data, and documentation of database modifications (audit logs). DCC is also responsible for validating and documenting standards compliance, database integrity checks, information security (individual user logins, permissions based on need, and encrypted data transmission), and data retrieval and export.

Weekly vulnerability detection scans of DCC computing resources are performed by a third-party vendor, which include full administrative credentials to perform maximum detection techniques. Real-time virus protection software is implemented and routine full system virus scans are performed.

14.5.1 Data Quality Assurance

The DCC has designed and implemented web-based data collection instruments in REDCap to support the data collection and analyses for this protocol. These instruments utilize real-time data type and rule-based validation, and skip logic techniques to prevent collection of erroneous interdependent data, and maximize the use of pre-defined selection options and computer-derived values to reduce capture of inaccurate data due to human error.

Selected data elements are pre-coded for statistical analysis as a part of the data collection instrument design and implementation. Most of these coded data are continuously available for reporting and extraction by the Data Manager and Biostatistics faculty and staff. Those selected elements that are unable to be coded automatically are coded routinely by DCC medical coding personnel.

Each user is provided an individual username and password to access REDCap for this protocol. REDCap uses a role-based permissions system to ensure that users are given access to the proper

information and operations necessary to their role in the protocol. Pursuant to applicable standards, REDCap automatically and non-destructively records all data collection entries/modifications and associated values along with the user account and date/time stamp information.

14.5.2 Standards Compliance of Data Management System

The REDCap system is implemented and supported by the DCC for the PRIORITIZE registry program. US FDA Title 21 Code of Federal Regulations (CFR) governs Food and Drugs. Part 11 sets forth the criteria under which the Agency considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper, and states that such records should be validated, should produce a time-stamped audit trail of data modifications, should require electronic signatures and should restrict access to authorized users. The REDCap Data Management system itself is validated by its developers. Additionally, the instruments and programming implemented for the PRIORITIZE registry will be validated to comply with the specified FDA recommendations. Validation of such systems documents that the system performs in an expected and predictable manner, and annual internal audits are performed to ensure compliance is maintained.

The PRIORITIZE Data Management systems are compliant with multiple Federal standards designed to ensure the safety, security and integrity of sensitive information.

14.5.3 Continuous Data Quality Monitoring

To help minimize the frequency of errors, the Data Manager conducts routine and ad hoc meetings with the Clinical Monitoring and/or Abstraction Core staff to discuss any consistently observed deficiencies in the use of the data management system and abstracted data. The DCC team maintains regular contact with the CDAS staff to address identified deficiencies. Also, provision of timely data quality reports will be an important aspect of the Data Management function. In addition to documenting exemplary performance, these reports will provide a basis for setting goals for high-quality data collection, and for tracking progress towards achieving those goals. Data queries will be generated by the DCC team in order to identify problems on an on-going basis. Such data checks will include, but are not limited to:

- Frequencies on selected variables by CDAS, to identify differences in the application or interpretation of study protocol or abstraction conventions;
- Tabulations and listings of incomplete or inconsistent responses on data collection forms; tabulations and listings of expected forms not received in a timely manner; and tabulations of clinical center error rates in data entry;
- Analyses of digit preferences for clinical measurements (e.g., blood pressure, weight, height) and other evidence suggesting inadequate or erroneous data entry; and
- The collection of repeated measures for quality control purposes as selectively implemented.

14.6 Training & Certification of Chart Data Abstraction Specialists (CDAS)

Designated CCC and Abstraction Core staff receive detailed protocol, REDCap and disease specific training as well as gain familiarity with the Study Reference Manual prior to being authorized for access to the PRIORITIZE data management system.

The DCC will monitor the centrally abstracted chart data from the data provided by all clinical sites through standard reporting and methods.

14.7 Monitoring Activities

DCC personnel in conjunction with the CCC closely monitor clinical center adherence to study protocol and data collection practices for complete and accurate research data. Monitoring is performed following an established Data Management and Clinical Monitoring Plan to facilitate the smooth conduct of the study. DCC personnel will have access to all study and patient documents and to clinical center personnel. All patient and study documents will be kept confidential. Identifiers such as patient name and address can be viewed by the DCC or CCC to facilitate study processes, including remote monitoring, but these identifiers will not be included on any datasets used for data analyses.

DCC personnel and CCC personnel meet regularly to discuss study status, recruitment, compliance with the protocol, clinical center participation, and other issues that arise during the course of the study. The DCC will provide statistical computations, reports, and recommendations to the Steering Committee.

The PRIORITIZE registry team will commission qualified resources to conduct monitoring of the data. Clinical site visits and data monitoring will be performed in accordance with the Clinical Monitoring Plan (CMP) Monitors will inspect the operations to ensure that:

- The protocol is followed and implemented in compliance with Good Clinical Practices;
- Accurate and complete records are maintained;
- Staff are trained, certified, and are performing the agreed-upon activities and not delegated to other unspecified staff.

All monitoring activities will be completed with a formal, written report. The report will summarize the findings and highlight all recommendations and action items.

15. HUMAN PARTICIPANT ISSUES

This study will comply with the Department of Health and Human Services (DHHS) Federal Policy for the Protection of Human Research Subjects, reflected in HHS regulation 45 CFR 46. This regulation includes the Common Rule and will rely on National Institutes of Health (NIH) GUIDANCE and its interpretation of the Common Rule. PRIORITIZE will observe individual site IRB and federal requirements for protection of human subjects and fulfilment of HIPAA in the same manner as the established HCV-TARGET network.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. The assurance of each staff member's education and training will be collected by the CCC regulatory director and/or qualified staff member and reviewed by the DCC monitors in accordance with ICH guidelines. Specifically, a CV (evidencing qualifications of investigators and sub-investigators) and medical license will be required of all staff members providing medical care to subjects prior to participation in the trial. A CV or equivalent form of verification of qualification to perform delegated duties will be required of all staff engaging in human subject research activities. In accordance with PCORI requirements, all key personnel are required to provide proof of completion of the NIH Protection of Human Research Participants module or equivalent training prior to participation in the PRIORITIZE project. The project manager, monitors of the DCC, and regulatory director will provide additional training and

education on the principles of Good Clinical Practice and protection of human research participants during site initiation visits and/or investigator meetings (in person and/or remote).

Sites will be provided a template consent form to modify according to local regulations and requirements. In order to ensure that site ICFs do not conflict with the template ICF and/or the protocol, the CCC regulatory staff will review all site ICFs prior to submission to local IRBs or Ethics Committee. Following review and approval of the site specific ICF, the study protocol, consent forms, and surveys/questionnaires will be submitted to each local IRB for review and approval. Any additional patient educational material specific to PRIORITIZE will also be submitted for approval prior to distribution. A site may not engage in PRIORITIZE human subject research activities until IRB approval has been forwarded to the CCC and the DCC and CCC have confirmed the site for initiation of study activities.

Given the epidemiology of HCV infection, participants enrolled in this study will include a diverse population including Black African Americans and Hispanics. It is anticipated that males will be more frequently enrolled than women also reflecting the epidemiology of this disease. We anticipate that the participants recruited from multiple sources, including community and tertiary referral populations, will capture the entire spectrum of HCV infection.

Consent for study participation will be obtained according to Section 6.1.

15.1 Potential Benefits/Discomforts and Risks/Subject confidentiality

Study sites and the CCC Chart Data Abstraction team will be responsible for the confidentiality of the data associated with participants in PRIORITIZE in the same manner they are responsible for the confidentiality of any patient information within their spheres of responsibility. In order to maintain subject confidentiality, all data forms used for the study data will be identified by a code. The link between the code and each subject will be kept in secure, password-protected file or locked files, if paper copy, accessible only to PRIORITIZE study staff. Any printed records will be kept in locked files at study sites and CCC with access limited to PRIORITIZE study staff. All study staff will identify participants by the coded identifier number generated at the study site. Clinical information will not be released without written permission of the participant, except as necessary for monitoring by the IRB or DCC and centralized abstraction at the CCC. Participants grant permission to share research data with these entities in the consent document. Federal regulations govern the protection of patient's rights relative to data confidentiality and use of research data.

Consent procedures and forms, and the communication, transmission and storage of patient data will comply with individual site IRB and federal requirements for compliance with HIPAA. The commercial central laboratory draw site and the associated testing facility may collect PHI from participants as part of the samples collection process.

15.2 HIPAA Privacy Rule Elements of PHI

Established in 1996, the U.S. Department of Health and Human services issued the Privacy Rule as part of the Health Insurance Portability and Accountability Act to establish a national set of standards for the protection of certain health information. This rule protects all "individually identifiable health

information" held or transmitted by a covered entity or its business associate in any form or media whether electronic, paper, or oral. A list of 18 Identifiers was established:

1. Names
2. All geographical subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code, if according to the current publicly available data from the Bureau of the Census: (1) The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and (2) The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.
3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older
4. Phone numbers
5. Fax numbers
6. Electronic mail addresses
7. Social Security numbers
8. Medical record numbers
9. Health plan beneficiary numbers
10. Account numbers
11. Certificate/license numbers
12. Vehicle identifiers and serial numbers, including license plate numbers
13. Device identifiers and serial numbers
14. Web Universal Resource Locators (URLs)
15. Internet Protocol (IP) address numbers
16. Biometric identifiers, including finger and voice prints
17. Full face photographic images and any comparable images
18. Any other unique identifying number, characteristic, or code (note this does not mean the unique code assigned by the investigator to code the data)

Records submitted for Centralized Abstraction and through RED-I are redacted for these PHI identifiers *except for dates of service/activities*. In instances where a PHI identifier other than a date of service is present on a redacted record delegated CCC personnel will redact that information.

Except where payment for research participation by the University of Florida's Human Subject Payment (HSP) Program is prohibited, payment for participation in this research study will be handled through the University of Florida's Human Subject Payment (HSP) Program. Subjects' name, address, date of birth, and social security number will be recorded and maintained in a confidential and secure manner on University of Florida's encrypted HSP system to facilitate compensation. This information will be reported to the appropriate University of Florida employees for making and recording the payment as required by law. This information will be separated from health information via additional passwords and access limited to PRIORITIZE site coordinator(s), UF Hepatology Research Staff, and the University of Florida's Human Subject Payment (HSP) Program. Additionally, subjects will be randomly assigned a specific identification (ID) number to protect subjects' identity.

16. DATA DISSEMINATION

Our stakeholders – which include patients, patient organizations, public and private payers, government agencies, health systems, clinical practice guidelines committees, pharmacy benefit managers and specialty pharmacies – share a strong commitment to collaborating in multiple ways to ensure dissemination and implementation of the findings. Our stakeholders have been invited to partner during the study to: 1) inform their community of the study and provide updates; 2) attend the Quarterly Pragmatic HCV Assembly calls; and 3) share in disseminating results. Further, our HCV-Patient Engagement Group and Patient Organization Partnership Committee will work with and have representation on the Steering Committee to plan and ensure dissemination of the findings.

In partnership with our stakeholders and in alignment with PCORI's Dissemination & Implementation Framework, we envision a multifaceted approach to assess the evidence and plan for suitable dissemination and implementation activities that can inform care-related decisions in a rapid and contextually appropriate manner. We will be able to utilize data and feedback obtained through patient engagement activities, quarterly assembly calls, patient interviews, patient surveys and patient town halls to develop patient-centered dissemination strategies and communicate the final findings in understandable, usable language and materials. Dissemination to patients will include sharing findings through our nine patient organization partners, which include The Caring Ambassadors Hepatitis C Program, NATAP, and The Hepatitis C Support Project/HCV Advocate, among others. These patient organizations have a strong social media presence and produce information resources such as newsletters, websites, information packets and more. As examples of their reach, Jules Levin and NATAP have a listserv of more than 400,000 clients, and HCV Advocate receives 600,000 website hits per week. We will work closely with PCORI and stakeholders to ensure the responsible release of data in accordance with our statistical plan as well as PCORI's process for the peer review and public release of research findings.

HCV-TARGET has a well-established publication and dissemination plan to translate study findings for broad clinical communities, including non-specialists. We will publish in peer-reviewed scientific journals that play a key role in influencing practice guidelines and policy decisions. Importantly, our stakeholders include the professional societies responsible for updating U.S. treatment guidelines (AASLD, IDSA). In addition, Drs. Nelson, Fried and Sulkowski have developed multiple continuing medical education (CME) programs related to hepatitis C, with a focus on clinical implementation of new treatment regimens. CME programs are an important mechanism for disseminating findings to clinicians. A multicomponent dissemination strategy for clinicians also might include development of supporting communication materials, such as evidence summaries or decision aids.

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