Statistical Analysis Plan (SAP) for Comparison of HERO SVR Outcome between DOT and PN Treatments

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Prepared by HERO Statistical Analysis Team
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Table of Contents

1 Introduction

The present statistical analysis plan is prepared for the multi-site Hepatitis C Real Option (**HERO**) study sponsored by PCORI (HPC-1503-28122; Clinical Trial Registration #: NCT02824640). The HERO is a pragmatic randomized clinical trial designed primarily to test difference in sustained viral response (SVR) outcome among people who inject drugs between two models of care: directly observed therapy (DOT) vs. patient navigation (PN). This statistical analysis intends to maximize transparency and reproducibility of the statistical analysis results and minimize potential biases due to indication of statistical analysis results. To this end, this plan is prepared and approved by the entire HERO study investigator team prior to the completion of main outcome data collection and cleaning which is anticipated to be accomplished by April 2020. This plan primarily focuses on the comparative analysis of SVR outcome after 12 week-long Hepatitis C treatment period with direct-acting antiviral medications. Plans for analysis of several secondary outcomes are also addressed.

2 Independent Parallel Analysis

To ensure reproducibility of statistical analysis results, two independent statisticians, one at University of New Mexico (UNM) and another at Clemson, will comply as closely as possible with the analytical plans detailed herein, which are reviewed and approved by the HERO investigators. They will analyze the primary outcome, SVR, independently and in a parallel manner, and compare their results. If their results are substantially different beyond a tolerable variation, then the two statisticians will examine each other's analytic strategy and software codes to reach a consensus. Final results will be reported upon agreement of the two statisticians. Investigators will not be involved in this process, and more importantly, data analysis will not be guided or influenced by the indications of results. Each aspect of data analysis such as cleaning, analysis, and output will be logged and archived for review.

3 Definitions of Study Analytic Samples

All study participants must meet the screening inclusion and exclusion criteria AND sign the consent form. These participants are defined as enrolled participants/sample. From these enrolled participants, the analytic sample for all statistical analysis will be defined in the following three categories:

3.1 Primary analytic sample

This primary analytic sample includes the enrolled study participants who were *randomized and initiated* treatments. This sample is referred to as the *modified* intention-to-treat (mITT) analytic sample. The participants who initiated treatment will consist of those who had intake of at least one dose of the medication after randomization.

3.2 Secondary analytic sample

This secondary analytic sample includes all enrolled study participants who were *randomized*. This sample is referred to as the intention-to-treat (ITT) analytic sample.

3.3 Per protocol analytic sample

This per protocol (PP) analytic sample includes the enrolled study participants who 1) were randomized; 2) initiated treatment; 3) complied with the randomly assigned models of care without cross over any time during the 12-week treatment; and 4) had SVR outcome data (yes vs. no). This sample is referred to as the per-protocol (PP) analytic sample. The PP sample will be a subset of the mITT sample which is in turn a subset of the ITT sample.

The intention-to-treat principle reflects the principle that once the intervention was randomly assigned to a participant, the participant's intervention assignment will not change in the analysis even if s/he crossed over the other intervention during the trial period or did not complete intervention activities. The application of this ITT principle reflects the real-world goal of the HERO study which is to treat all PWID with HCV (i.e., all randomized individuals). However, as the HERO study was designed as of a pragmatic randomized clinical trial (RCT), the ITT sample will not be used as the primary analytic sample because the outcomes are defined conditions on the initiation. Furthermore, the primary (SVR) and several of the other secondary outcomes (treatment completion, adherence) are only relevant among those who initiated treatment.

All statistical analyses proposed in the present SAP will be repeated for each analytic sample. Comparison across the three analytic samples will be compared to assess internal or external validities or limitations of the study findings. In particular, analysis of the secondary ITT sample will provide estimates of milestones along the HCV cascade of care by study arm and in the full sample. All statistical analyses will be conducted using SAS v9.4 and R 3.5 or higher, and a two-tailed significance level of 0.05 will be applied to all testing and confidence intervals.

4 Preliminary Data Analysis of Baseline Characteristics

4.1 Baseline Characteristics

We will consider the following baseline characteristic to characterize the HERO study participants [To be further determined]:

- Demographic Characteristics: Gender, Ethnicity, Race, Age, Education, Marital/ Cohabitation status, Potential Transportation Barrier, Housing status, Employment Status
- Clinical Characteristics: Clinical Setting (OTP or CHC), Cirrhosis, Anxiety Symptoms, Depression Symptoms, HIV/HCV coinfection, HCV-treatment history (Naïve or Experienced), HCV-related information (Genotype, HCV Viral Load), Other infectious

Diseases (HV, HBV, HAV), Medication for Opioid Use Disorder (buprenorphine, methadone)

- Behavior Characteristics: Hazardous alcohol drinking, Injection behaviors (duration, frequency, last drug injection), Substances injected (mixture of heroin and cocaine, mixture of methamphetamine and heroin, cocaine, methamphetamine, heroin, crack, fentanyl), Used drug type (amphetamine, benzodiazepine, , cocaine, opiate, methamphetamine, oxycodone, cannabis/THC)

Detailed information on the baseline characteristics including their definitions and classifications along with all data sources for each characteristic are displayed in Table 1. Briefly, for the baseline demographic factors, the data collected at enrollment visit (consent and demographic survey) will serve as the primary data sources. Data from the screening will serve as the secondary data sources. For the other clinical factors, the data at the screening (chart review 1), enrollment (Chart review 2), or baseline will serve as the primary data sources. If the data are not available at the primary sources, they will be replaced by the secondary data such as the Visit 1/Baseline (chart review 2) research visit data. For the behavior characteristics, the data at the screening or baseline will be used as the primary and only data sources. In short, the data collected at three different time point—screening, enrollment, and baseline/V1 visit (2 week period)—will serve as the primary, or secondary data sources depending on baseline characteristics in effort to minimize missing values.

Table 1. Baseline characteristics

Characteristic	Category	DOT (N=375)	PN (N=379)	Primary source	Secondary source
Gender[1]				E	S
	Female				
	Male				
	Transgender or Gender Non-conforming				
Age[2]				E	S
	Mean (SD)				
	Median (Q1, Q3)				
Race[3]				E	S
	White/Caucasian				
	Black/African American				
	Other				

Characteristic	Category	DOT (N=375)	PN (N=379)	Primary source	Secondary source
Latino/Hispanic Ethnicity[4]				E	S
Marital/cohabitation Status[5]				E	
	Single/Separated/Divorced/Widowed				
	Married/living together as married				
	Other				
Education[6]				E	
	Less than HS				
	HS diploma or GED				
	Some college or more				
Living situation[7]				E	
	Street/outdoors				
	Shelter				
	Someone else's apartment, house or room				
	*Institution**				
	Own/rent apartment, house, or room				
	Other				
	*Unstable housing**				
Availability of transportation[8]				E	
Yes					
Maybe, if I can get a ride					
Maybe, If public transportation is available					
No					
Employed with a regular job or informal work[9]				E	
Clinical Setting[10]				E	S
	OTP				
	CHC				
Any medication for OUD in the past 3 months[11]				B	

Characteristic	Category	DOT (N=375)	PN (N=379)	Primary source	Secondary source
	Buprenorphine				
	Methadone				
	None				
Depressive symptoms[12] (PHQ-9) [Mean (SD)]				B	
PHQ-9 Severity				B	
	Mild (<10)				
	Moderate (10-14)				
	Moderately severe/severe (>14)				
Anxiety symptoms (GAD-7)[13] [Mean (SD)]				B	
GAD-7 Severity[13]				B	
	Mild (<10)				
	Moderate (10-14)				
	Moderately severe/severe (>14)				
HCV Treatment History[14]				S	
Naive					
Experienced					
Cirrhosis[15]				CR1	CR2
Genotype (available)[16]				CR2	
Genotype				CR2	
	Type 1				
	Type 2				
	Type 3				
	Type 4				
	Mixed				
HCV viral load, IUs/mL (available)[17]				CR1	CR2
HCV viral load, IUs/mL				CR1	CR2
	Mean (SD)				
	Median (Q1,Q3)				

Characteristic	Category	DOT (N=375)	PN (N=379)	Primary source	Secondary source
HIV co-infection (available)[18]				CR2	
HIV co-infection (positive)				CR2	
HIV viral load (available)				CR2	
HIV viral load, <200copies/mL				CR2	
HIV viral load, ≥200copies/mL				CR2	
HBV surface antigen(available)[19]				CR2	
HBV surface antigen (positive)				CR2	
Hazardous alcohol use[20]				B	
Last drug injection (within 3 months from screening)[21]				S	
0-4 weeks					
5-8 weeks					
9-12 weeks					
Number of days injected drugs in the past 3 months[22]				B	
	Mean (SD)				
	Median (Q1, Q3)				
	Missing				
Times injecting drugs a day[23]				B	
	Mean (SD)				
	Median (Q1, Q3)				
	<3				
	≥3				
	missing				
Substances injected in the past 3 months[24]				B	
	Mixture of cocaine and heroin [A]				

Characteristic	Category	DOT (N=375)	PN (N=379)	Primary source	Secondary source
	Mixture of methamphetamine and heroin [B]				
	Heroin [C]				
	Methamphetamine [D]				
	Cocaine [E]				
	Crack [F]				
	Fentanyl [G]				
	Poly-substances [H]				
Urine drug screen positive at baseline visit[25]				B	
	Amphetamine				
	Methamphetamine				
	Benzodiazepine				
	Cocaine				
	THC/Cannabis				
	Opiate				
	Oxycodone				
	Any drug [15]				

Notes: S: Screening; E: Enrollment; B: Baseline; CR1 Chart review 1

4.2 Comparisons of baseline characteristics

First, the distributions of all baseline characteristic variables will be examined using graphical or descriptive statistics to identify any values out of range. When identified, out of range values will be found in the original record, compared and corrected if needed. Second, although by the stratified randomization design, each arm will be distributed across site/city, clinic type (OAT and CHC) and stage of liver disease (cirrhosis vs. no cirrhosis), the success of randomization will be verified by comparing baseline characteristics between the two model of care arms, PN and DOT. Continuous variables will be compared between arms using t-tests or Mann-Whitney tests, and categorical variables will be compared using chi-square or Fisher's exact tests. We will provide only descriptive statistics on the baseline characteristics between arms in a table without reporting of p-values following the CONSORT guideline.

5 Analytic plan for the primary Sustained Viral Response (SVR) outcome

5.1 SVR Hypothesis

Among participants who *initiate* HCV treatment, rate of SVR at 12 weeks post treatment completion will be higher in the DOT vs. PN arm.

5.2 SVR determination process

SVR will be determined for each participant in the ITT sample, and thus for the mITT and PP samples as well. First, the time window for relevant viral load data for determination of SVR is set at between post-EOT (end of treatment) 10 week (or 70 days) and post-EOT 1 year (or 365 days). This time frame is further divided into two widows: the primary time window (post-EOT 70 days to 98 days) and the secondary time window (post-EOT 99 days to 365 days) (Figure 1). SVR status will be declared based on viremia data collected from the medical chart reviews or bio-repository data and classified into the following three categories: Success, Failure, and Undetermined. Detailed algorithm for the SVR determination process within the primary and secondary time windows is described in Figure 2.

Figure 1. Hero Study Post-EOT Timeline for SVR Determination

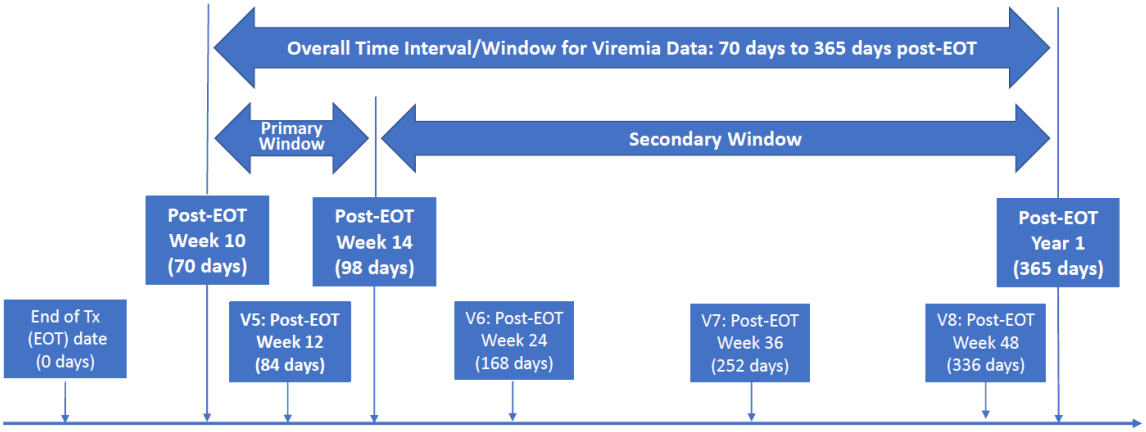
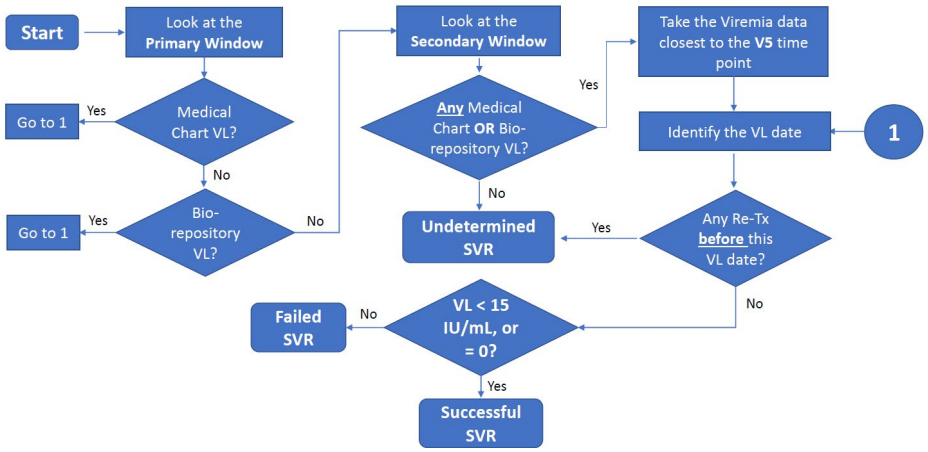


Figure 2. SVR Determination Process



5.3 Handling undetermined/missing SVR data for primary analysis

5.3.1 mITT analysis

a. Primary approach: The undetermined SVR will be treated as SVR failure.

b. Secondary approach: The undetermined SVR imputed by a fully specific conditional specification multiple imputation method. This imputation will be made stratified by the study arm. In each arm, overall adherence and the total duration of treatment will be used as predictors of the imputation model. Of note, the imputation will NOT be applied to undetermined SVR due to death; in this secondary approach, deaths will still be treated as SVR failure.

5.3.2 ITT analysis

a. Primary approach: The undetermined SVR will be treated as SVR failure.

b. Secondary approach: Any imputation will be not be made to the participants who did not initiate or died during the treatment period. For the other participants, we will use the imputed SVR that was generated for the mITT sample above.

5.3.3 Per-protocol analysis

The missing SVR will be excluded by the definition of per-protocol sample. Therefore, the analysis will use completely observed SVR, successful or failed, for this analysis without necessity of imputation.

5.4 Statistical Model

Multivariable logistic regression will be applied to test the overall effectiveness of DOT or PN on the SVR (success vs. failure) as the primary outcome. The arm indicator will serve as the primary predictor. The CONSORT and ICH-9 statistical analysis guidelines suggest that, any baseline characteristics, even if significantly unbalanced between arms, should not be included in the multivariable logistic model since baseline imbalance could be due to chance rather than systematic bias in randomized studies but include as the covariates the randomization stratification variables. In the HERO study, they are: site/city, clinic type (OAT and CHC) and stage of liver disease (cirrhosis vs no).

The primary mITT sample, nonetheless, might no longer represent a randomized pool of participants since the characteristics of participants who initiated treatments may be unequal between the two models of care which may have differential effects on triggering treatment initiations due to difference in modalities of treatment initiation and delivery. Therefore, there could exist baseline characteristics that are unbalanced beyond chance among initiated participants between the two arms. We will declare imbalance if a baseline characteristic is significantly different between the two arms with a two-sided p-value < 0.01 considering the multiplicity of testing. As such, we will include unbalanced baseline characteristics for adjusting purposes in multivariable models in addition to the randomization stratification variables, resulting in the following model:

$$\text{Logit}(P(SVR)) = b0 + b1*TRT + b2*Site1 + \ldots + b8*Site7 + b9*Clinic\_Type + b10*Cirrhosis + \text{Unbalanced Covariates}$$

We will consider exploring other methods to adjust potential imbalance using propensity scores or inverse probability weighting.

For the analysis of the secondary ITT sample, we will only include the randomization stratification variables following the CONSORT and ICH-9 statistical analysis guidelines since the ITT samples are purely randomized participants, resulting in the following model:

$$\text{Logit}(P(SVR)) = b0 + b1*TRT + b2*Site1 + \ldots + b8*Site7 + b9*Clinic\_Type + b10*Cirrhosis$$

For the analysis of PP model the approach applied to the analysis of the mITT sample will be applied.

Review of the monthly enrollment reports during the conduct of the study, however, consistently revealed that few participants have cirrhosis to the extent that there are sites and clinics without any randomized participants with cirrhosis. This imbalance raises a concern with respect to the logistic model fitting which may not result in convergence in regression coefficient estimation algorithms due to a potentially ill-conditioned data matrix. If this occurs, we plan to

remove the cirrhosis term in the above model and fit the following model as the primary multivariable model that include only sites and clinic types for adjusting purpose.

$$\text{Logit}(P(SVR)) = b0 + b1*TRT + b2*Site1 + \ldots + b8*Site7 + b9*Clinic\_Type + \text{Unbalanced Covariates}$$

We will report the adjusted odds-ratio (OR) with a 95% confidence interval (CI) for the estimate of the DOT vs. PN effect on SVR. We will also compute 95% CIs for the overall and arm-specific SVR rate using an exact (Clopper-Pearson) method to compare with results from other trials. Again, this analysis will be repeated for each of the three analytic samples albeit with different adjusting variables depending on the constituency of the samples: mITT, ITT and PP.

5.5 Power analysis

The HERO study was planned to recruit N=300 participants in each arm in the mITT sample. Considering the base 80% SVR rate in the PN arm, a minimum difference of 9% between the two arms will be detected (i.e., 89% vs. 80%, OR=2.1) with the planned sample size in a multivariable logistic regression model in which adjusting variables explain 10% of variation in the predictor variable. This study posits that a >9% difference in SVR between the PN and DOT groups will be clinically significant based on studies that showed that SVR in treatment naive patients was >90%.

6 Subgroup Analysis

Subgroup analysis will be conducted to assess potential heterogeneity of models of care effect across the levels of subgroups (section 6.1). The subgroup analysis will estimate and test: 1) main subgroup effect (section 6.2.1); and 2) the interaction between subgroup and the models of care to assess both between-arm and within-arm subgroup effects (section 6.2.2).

6.1 Subgroups to be compared

The primary subgroups and their levels are as follows:

- Demographic factors:
    - Sex: Males vs. Females
    - Age: <30 vs. ≥30
    - Race/Ethnicity: African American vs other; White vs. Other
    - Ethnicity: Latino (Yes vs. No)
    - Employment: Employed vs. Unemployed
    - Education: ≤HS diploma vs >HS diploma

  - Married/Co-habitating vs. Other
  - Housing: Unstable vs. stable
  - Ability of transportation vs. Inability
- Clinical factors:
  - Opioid agonist treatment (OAT) clinic vs. community health clinic (CHC)
  - Any medication for OUD in the past 3 months: methadone/buprenorphine vs. none
  - HIV Co-Infection (yes vs. no)
  - HIV viral load: <200copies/mL vs. ≥200copies/mL
  - HCV Genotype (3 vs other)
  - HBV Co-infection: yes vs. no (+ vs. -)
  - Cirrhosis (yes vs. no)
  - Depression (severe/moderate vs. mild/none)
  - Anxiety (severe/moderate vs. mild/none)
  - HCV Treatment naïve vs. experienced
- Alcohol and Drug use:
  - Hazardous alcohol at baseline (yes vs. no)
  - Hazardous alcohol during treatment (yes vs. no)
  - Amphetamine at baseline (UTOX): Yes vs. No
  - Amphetamine during treatment (UTOX): Yes vs. No
  - Benzodiazepine at baseline (UTOX): Yes vs. No
  - Benzodiazepine during treatment (UTOX): Yes vs. No
  - Cocaine at baseline (UTOX): Yes vs. No
  - Cocaine during treatment (UTOX): Yes vs. No
  - THC/Cannabis at baseline (UTOX): Yes vs. No
  - THC/Cannabis during treatment (UTOX): Yes vs. No
  - Opiate at baseline (UTOX): Yes vs. No
  - Opiate during treatment (UTOX): Yes vs. No

- Oxycodone at baseline (UTOX): Yes vs. No
- Oxycodone during treatment (UTOX): Yes vs. No
- Any drug screen + at baseline (UTOX): Yes vs. No
- Any drug screen + during treatment (UTOX): Yes vs. No

- Injecting Behaviors:
  - Last drug injection at baseline: within 5-8 weeks vs 0-4 weeks
  - Last drug injection at baseline: within 9-12 weeks vs 0-4 weeks
  - Times IDU a day at baseline (≥2 VS <2)
  - Times IDU a day during treatment (≥2 VS <2)
  - Times IDU a day at baseline (≥3 VS <3)
  - Times IDU a day during treatment (≥3 VS <3)

Note: Additional subgroup analyses will be conducted based on investigator-driven proposals on concept sheets

6.2 Statistical Models

Subgroups will be defined based on the above factors and. Estimates of treatment effects in terms of adjusted ORs and 95% CIs will be obtained separately in all subgroups using logistic regression models adjusting for the study arm and the sites. We will not include the other stratifying variables or unbalanced covariates in these subgroups analysis because they themselves will also serve as subgroups to be compared. In short, for all subgroup analysis, we will apply a consistent modeling framework adjusting only for the study arm and the sites.

6.2.1 Main subgroup effects

The main effect of subgroup indicators (e.g., OAT vs. CHC) will be assessed via comparing outcome between levels of each subgroup in multivariable models adjusting for the care model arms and site, that is, the multivariable logistic regression model that include: a subgroup indicator, site and the arm indicator in the following form:

$$\text{Logit}(P(SVR)) = b0 + b1*\text{Subgroup Indicator} + b2*TRT + b3*Site1 + \ldots + b9*Site7.$$

The analysis results will be graphically displayed in a forest plot.

6.2.2 Assessment of heterogeneity of models care effect across subgroups

The following multivariable model will be used to both: 1) estimate and test DOT vs PN effects in each subgroup (i.e., DOT vs. PN in each of OAT and CHC); and 2) estimate test Subgroups effects in each of DOT and PN arms (OAT vs. CHC in each of DOT and PN arms).

$$\text{Logit}(P(SVR)) = b0 + b1*\text{Subgroup indicator} + b2*TRT + b3*\text{Subgroup indicator}*TRT + b4*Site1 + \ldots + b10*Site7$$

The primary interest of this subgroup analysis will be estimating the DOT vs. PN effect on SVR in terms of point (i.e., odds-ratio) and interval estimates (i.e., 95%CI) and testing significance of DOT vs. PN effects in each group. The analysis results will also be graphically displayed in a forest plot. The secondary interest will be testing significance of the interaction term that represents a difference in DOT vs. PN effect on SVR between subgroups.

6.3 Power analysis for subgroup analysis

For testing the main effect of subgroup levels (eg, OAT vs. CHC) on the SVR outcome with the planned N=600 mITT sample size, the minimally detectable effect size will be approximately 9%-point difference between the subgroup levels which is the same as the power analysis addressed in section 4.5.

For testing significance of DOT vs. PN in each subgroup (e.g., OAT or CHC), however, the minimally detectable effect size of DOT vs. PN will depend on the sample size of each subgroup. For instance, if we assume that a subgroup (e.g., OAT) has 50% of the total mITT sample (i.e., N=300) and that a base SVR rate is 80%, then ≥12% difference will be detected in a multivariable logistic regression model in which adjusting variables explain 10% of variation in the predictor variable. This power analysis also applies to detect binary factors associated with outcome from within-arm subgroups analyses (e.g., OAT vs. CH in DOT or PN arm) since the mITT sample size of each arm will be N=300. For subgroups with smaller sample sizes, the minimally detectable effects sizes will be larger. For example, some of our subgroups will be as small as 20% (N= 120) of the sample (e.g., HIV/HCV coinfected), minimum effect sizes of SVR are larger at ≥157%.

7 Exploratory Mediated DOT or PN effects

Mediator analysis will be conducted to identify potential mediators between the DOT/PN effect and each of the SVR. A mediator will be a variable whose value changes or occurs between the baseline and the end of the study; for example, reduced shame, changes in social support, and increased self-efficacy. The potential mediating effects will be assessed by differences in DOT or PN effect sizes depending on outcome between with and without a potential mediator variable in statistical models. Their significance will be tested following the Baron and Kenny mediation test principle. The choice of specific potential mediators will be determined based on discussion with HERO investigators.

8 Analysis of other secondary outcome definitions and analysis plan

8.1 Treatment initiation

Treatment initiation status will be declared "yes" if a participant had intake of at least one dose of the medication after randomization, and "no" otherwise. By this definition, there will be no undetermined treatment initiation status, and all mITT and PP sample will have treatment initiation. Therefore, the analytic sample for the treatment initiation will be the ITT sample only.

8.2 Treatment initiation hypothesis

A higher proportion of patients in the PN arm will initiate treatment compared to the DOT arm.

8.2.1 Statistical Model

All statistical procedures and models applied to the analysis of SVR detailed above will also be applied except for the missing data imputation which is unnecessary. By the definition of treatment initiation, only ITT sample will be analyzed.

8.2.2 Power analysis

We hypothesize that a higher proportion of patients in the PN arm will initiate treatment compared to the DOT arm, which is expected to have 60% treatment initiation rate. With the planned N=1000 ITT sample size, we will be able to detect a minimum of 12% difference (i.e., 60% vs. 72%, OR=0.58) in any outcome in a multivariable logistic regression model in which confounding variables will explain 10% of variation in the predictor variable.

8.3 Treatment Completion

The primary treatment completion outcome (100% completion) will be declared "yes" if a participant went through at least 84 days of treatment from his/her start treatment date to end treatment date regardless of adherence to the medications. By this definition, there will be no undetermined treatment completion status in any of the three analytic samples. The secondary treatment completion outcome (80% completion) will be determined based on whether a patient was treated for 68 days at least, which is 80% of the prescribed 84 treatment days, i.e., whether or not the length between the start and end dates (both inclusive) are greater than or equal to 68 days. The third treatment completion outcome will be the number of treatment days within the 84-day window on a continuous scale. Comparisons of median treatment days, third completion outcome, will be conducted as a secondary analysis.

8.3.1 Treatment completion hypothesis

Patients in the DOT arm will have higher treatment completion rate compared to the PN arm.

8.3.2 Statistical Model

All statistical procedures and models applied to the analysis of SVR detailed above will also be applied except for the missing data imputation which is unnecessary. All of ITT, mITT, and PP samples will be analyzed.

8.3.3 Power analysis

We hypothesize that patients in the DOT arm will have higher treatment completion rate, compared to the PN arm, which is expected to have 80% completion rate. Like SVR rates, we will be able to detect a minimum of 9% difference in completion rates between the two arms (i.e., 89% vs. 80%, OR=2.1) with the planned mITT sample size of N=100 in each study arm.

8.4 Treatment adherence

The primary data source for the treatment adherence will be the electronic blister-pack data. Blister-pack daily adherence dose will be converted to weekly (or biweekly) adherences rate in percentages, i.e., how many daily intakes per week (or per two weeks). This weekly or bi-weekly rate will be the primary data to be analyzed for testing significance of difference in repeatedly-measured adherence between the two study arms during the treatment period. Self-reported adherence will also be analyzed as a secondary analysis.

8.4.1 Treatment adherence hypothesis

Participants in the DOT arm will have higher blister-pack daily-dose weekly adherence rate, compared to the PN arm.

8.4.2 Statistical Model

Mixed-effects linear model with the study as the primary predictor will be applied to the analysis of the blister-pack adherence data adjusting for the randomization stratification variables: sites, clinic types and cirrhosis status. This analysis will be applied to mITT and PP sample but not to ITT sample.

8.4.3 Power analysis

Per the weekly adherence percentage outcome, standardized effect sizes (mean difference divided by a pooled SD) greater than 0.2 will be detected by the mixed effects linear models regardless of magnitude of within-subject outcome correlations overt time.