The Patient-Reported Outcomes Project of HCV-TARGET ("PROP UP")

NCT02601820
May 13,2016

Study Protocol, version 1.0, 30Aug2015, PROP UP

Revised Protocol, Version 2.0, 24Sep2015, PROP UP

Revised Protocol, Version 3.0, 13May2016, PROP UP

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PCORI Contract# CER-1408-20660

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Changes

Revised Protocol, Version 3.0	13May2016	Based on the current landscape of HCV treatment options and feedback from investigators and the research team, the following changes/modifications will be incorporated into the PROP UP protocol:
		
		• Based on changes/anticipated changes in treatment practices, the scope of this study has changed in order to capture the most accurate information on recent treatment practices. The brief summary has been updated to reflect the overall changes in the study protocol.
		• Updated Section 1.0, Introduction, to reflect recent changes in HCV treatments. Several new DAA medications have been FDA approved but not extensively evaluated for long-term outcomes using patient reported outcomes.
		• Updated Section 2.0, Study Rational, to describe that PROP UP will evaluate, characterize and compare the short-term and long-term harms and benefits associated with several HCV treatment regimens.
		• Updated Section 3.1, Specific Aims, to reflect the fundamental protocol changes. The study will be focused on characterizing several HCV treatment regiments in terms of many harms and benefits captured via patient-reported outcomes collected before, during and after HCV treatment.
		  ○ Updated Aim 1 to explain the study will evaluate changes from baseline to time points during treatment in order to characterize harms associated with each of the treatments. The study uses several different measures, and adds patient-reported pre-existing medical conditions to list of the measures.
		  ○ Updated Aim 2. This aim will evaluation the difference in medication adherence between patients with and without a history of mental health/substance abuse by evaluating different measures as explained in the protocol.
		  ○ Updated Aim 3 to characterize short-term benefits of cure in the combine sample of patients.
		  ○ Updated Aim 4 to include pre-existing medical conditions and HCV-functional status, and the differences in all measures between patients with and without cirrhosis on various treatment regimens.
		• Added Section 3.2, Auxiliary Aims to describe that the study will examine a number of benefits and harms associated with DAA treatment and viral cure as described in the previous aims as well as use the data to examine similarities and differences between treatment regimens using causal inference methods.

		• Updated Section 4.2, Clinical Collaborating Settings, to include ninth site, UC-Davis in Table 1: Location of Liver Centers Participating in PROP UP. • Updated Section 4.31. Inclusion Criteria, with expanded inclusion criteria. Any HCV genotype is now eligible. Patients on the follow regimens are also eligible: sofosbuvir/ledipasvir (Harvoni®) with or without ribavirin, ombitasvir/paritaprevir/ritonavir with dasabuvir (Viekera Pak®), VPK) with or without ribavirin, elbasvir/grazoprevir (Zepatier®) with or without ribavirin, daclatasvir/sofosbuvir, with or without ribavirin (DAC/SOF), sofosbuvir/velpatasvir (SOF/VEL). • Updated section 4.3.2, Exclusion Criteria, to emphasis that patients participating in a pharmaceutical-sponsored trial of hepatitis C treatment will not be eligible. • Updated section 8.1, Procedures for Baseline PRO Data Collection, to add a sentence that participants will be reminded their answers are confidential before each survey. Also added that participants may complete surveys over the phone with research coordinator as needed at baseline. • Updated Table 2 in Section 8.2, Procedures for Baseline Collection of Clinical and Lab Data for the following: (a) add the new treatment regimens and prescribed treatment duration of 16 weeks, (b) update HIV status to collect HIV test conducted and HIV results status, (c) add stigma scale. • Updated Section 12.0, Participant Reimbursement, to reflect that UNC or subsites will reimburse subjects, aided by the REDCap system and records of reimbursement should be retained by the party responsible for paying the participant. • Updated Table 5 in Section 13.0, Clinical and Lab Data Collection at 12 Weeks Post-Treatment top add 16 weeks or other to Actual Treatment Duration in the table. • Updated Section 15.0, sub-sections 15.2 through 15.10 have been overhauled to reflect overall changes in the statistical analysis plan for this study. Updates include: description of the analysis of PRO changes from baseline as a function of subgroup and/or treatment regimen, description of the supportive longitudinal analysis and interpretation of changes from baseline, strategies for analysis of subgroup heterogeneity of treatment effects, and an overview of the four planned milestone manuscripts from this dataset. • Updated Section 15.12, Overview of Sample Size Considerations, to adjust the sample size considerations. • Added Appendix for Sample Size Analyses on page 34 of the protocol to provide tables and graphs to supplement the statistical analysis plan for the study. • Updated protocol with grammatical and minor content clarification changes through the entire document.

Revised Protocol, version 2.0	23Sep2015	Based on Investigator feedback from a recent Site PI conference call on 22Sep2015, the following changes/modifications will be incorporated into the protocol: • Based on current treatment guidelines, the protocol is being updated to include the enrollment of patients who are prescribed any "Harvoni-containing regimen" (e.g., Harvoni + Ribavirin). Section 4.3.1: Inclusion Criteria, Section 4.3.3: Discontinuation of Subjects from Study, Section 2: Study Rationale, Section 3: Study Aims, Section 6: Recruitment, and Section 8.2: Table 2 - Clinical and Laboratory Data Collection at Time of Consent have all been updated to reflect this change. • Clinical judgment suggests that some patients may tend to under-report infectious disease status, specifically HIV. The study will continue to collect patient-reported HIV status, but will also confirm HIV status via the patient's medical record and extraction the HIV antibody (Anti HIV) for verification. Section 8.2: Table 2 - Clinical and Laboratory Data Collection at Time of Consent has been update to reflect this change. • Based on clinical experience at each site, it may take up to 90 days to receive prior authorization of medications and for patients to initiate treatment. The baseline PRO assessment window will therefore be increased from 45 to 90 days prior to start of treatment to allow adequate time for treatment approvals and initiation of therapy. Section 8.1: Procedures for Baseline PRO Data Collection, Section 9: Enrollment Criteria and Section 10: PRO Data Collection Time Points have been updated to reflect this change. • The language has been clarified that patients must be 21 years of age or older (no upper limit) to be included in the study. The Brief Summary, Section 4.3: Study Population and Section 4.3.1: Inclusion Criteria have been updated to reflect this change. • Based on site feedback and in order to reduce missing data points from baseline assessment, the timeframe for valid HCV Viral Load has been expanded from 3 months to 12 months prior to consent. The timeframe for valid Aspartate Aminotransferase, Alanine Aminotransferase, Albumin, Total Bilirubin, Creatinine, International Normalized Ratio, Platelets and Hemoglobin lab tests has been expanded from 3 months to 6 months prior to consent. HCV genotype is not time-sensitive; most recent test should be extracted. Section 8.2: Table 2 - Clinical and Laboratory Data Collection at Time of Consent has been update to reflect this change.
Original Protocol, version 1.0	30Aug2015	Not applicable

CONFIDENTIALITY STATEMENT

This PROP UP study protocol is the confidential and proprietary information of the University of North Carolina at Chapel Hill (UNC). By reviewing this document, the investigator agrees to keep it confidential and to use and disclose it solely for the purpose of conducting PROP UP. Permitted disclosures will be made only on a confidential basis within your institution or to your IRB. Any other use, copying, disclosure or dissemination of this protocol is prohibited unless authorized by the UNC investigators. Supplemental information that may be added to this protocol during the study is also confidential. Please provide a copy of this study protocol to research personnel who will be directly working on the PROP UP study.

BRIEF SUMMARY

Title of Study: The Patient-Reported Outcomes Project of HCV-TARGET ("PROP UP")

Newer, more effective all-oral regimens for hepatitis C viral (HCV) infection have been approved in recent years and more are expected in the future. Minimal patient-centered outcome research (PCOR) data are currently available for the majority of these new drug regimens and enormous evidence gaps remain. In-depth information about these regimens is critical to informed decision-making, patient-provider communication, and patient adherence. Regimens may be relatively similar on SVR rates, but may differ on other short-term and long-term harms and benefits that matter to patients making treatment decisions. Data collected from pharmaceutical-sponsored trials do not provide all the answers, nor do their data represent what will happen when a broad spectrum of patients are treated in real-world practice. Trials also exclude vulnerable subgroups, focus mainly on short-term efficacy and clinician-rated adverse events, rarely obtain the patient's perspective, and do not investigate long-term harms of treatment or benefits of viral cure. Therefore, obtaining the requisite information in order to make informed decisions may prove challenging to patients and providers. Given these limitations, patient-centered outcomes research (PCOR) studies that evaluate short-term and long-tern treatment harms and benefits that matter most to patients, are needed.

PROP UP is funded by The Patient Centered Outcomes Research Institute (PCORI). PROP UP is a multi-centered patient-centered outcomes study designed to evaluate, characterize, and compare several patient-reported outcomes (PROs) during and after treatment for HCV with newly approved all-oral regimens. PROP UP uses a prospective, observational cohort study design to collect PRO data before, during and after HCV treatment to rigorously evaluate HCV-associated symptoms, treatment side effects, medication adherence, out of pocket costs, and long-term benefits of cure and harms of treatment in various HCV treatment regimens and among important patient subgroups. PROP UP was designed with significant involvement from patients with the disease and is a collaborative effort between behavioral and biomedical researchers, a HCV Patient Engagement Group (HCV-PEG), and a patient advocacy organization (HCV Advocate).

Nine U.S. liver centers will collaborate to conduct PROP UP. Approximately 1920 patients diagnosed with chronic HCV will be consented and will complete baseline PRO assessments. Patients who are 21 years of age, infected with chronic HCV, and prescribed one of several directing acting antiviral (DAA) treatment regimens for chronic HCV will be recruited. We anticipate that approximately 15%-20% of the 1920 patients who are consented will not commence HCV therapy, primarily due to insurance denials. Therefore we intend to enroll 1600 patients into longitudinal data collection. Enrollment criteria will include informed consent, completion of baseline PRO surveys, and administration of one dose of a prescribed regimen. These 1600 participants will be followed up to 1 year after HCV treatment ends. Participants will complete several PRO surveys at the following 5 assessment periods: (T1) Baseline, (T2) week 4 on-treatment, (T3) last 2 weeks on-treatment, (T4) 3 months post-treatment, and (T5) 12 months post-treatment for a total study duration of up to 20 months. PRO survey data will be collected via 3 options, selected by each participant: personal technology (home computer, tablet, smartphone) into web-based data capture system; phone-administered surveys with the UNC Call Center; or as a last resort, computer at regular clinic visits. PROs surveys are designed to measure HCV-associated symptoms, pre-existing conditions, treatment side effects, functional status, medication adherence, and out of pocket costs.

Longitudinal data collection of multiple novel PROs before, during and after treatment for HCV are being collected to better understand a variety of issues that are important to patients, clinicians, and stakeholders. Specifically, we will evaluate: (a) prevalence of pre-existing baseline symptoms associated with HCV; (b) the development of new onset treatment side effects and exacerbation of pre-existing symptoms during HCV treatment; (c) medication adherence and out of pocket costs related to HCV treatment; (d) changes in HCV-associated symptoms and functional status in patients who are cured; and (e) long-term patient-reported harms associated with treatments and long-term benefits associated with viral cure.

Study results will be disseminated via partnership with patient advocacy organizations and the HCV-TARGET network, as well as through traditional scholarly output. The findings from this study will help patients, providers, and stakeholders involved in decision-making by providing them with novel information they need to decide whether or not to proceed with HCV treatment and if so, what the short-term and long-term benefits and harms of HCV treatment, may be.

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1 INTRODUCTION

Chronic Hepatitis C virus (HCV) causes numerous liver-related complications and death, leading to tremendous burden on millions of people and the US healthcare system[1-3]. HCV kills >12,000 people per year in the US from liver-related complications such as liver failure, cirrhosis, liver cancer[4]. Over the course of 20-30 years, 20% of patients will develop life-threatening cirrhosis and 10% will develop liver cancer[5]. Morbidity and mortality rates are expected to increase dramatically in the next few decades as Baby Boomers suffer the long-term consequences of HCV[6].

People infected with chronic HCV also frequently suffer from chronic, systemic symptoms, other chronic conditions, and poorer quality of life, compared to the general US population[7,8]. In addition to liver-related morbidity and mortality, many people with HCV complain of diffuse physical (e.g., fatigue, abdominal pain, nausea, poor appetite, joint/muscle achiness) and neuropsychiatric symptoms (e.g., mental fatigue, depression, irritability, insomnia, cognitive impairment)[9]. Many patients with HCV also have higher rates of comorbid conditions (e.g., psychiatric, addiction, diabetes, skin, HIV, renal) compared to the general population[2,9-12]. Not surprisingly, people with HCV report poorer health-related quality of life (HRQOL) on many domains of functioning compared to their healthy counterparts. This relationship remains significant even after controlling for substance abuse history[13,14]. The reasons for poor HRQOL are complex and likely multi-factorial, but may include symptoms due to chronic systemic viral inflammation of the central nervous system, comorbid conditions, feelings of social stigma, and constant health-related anxiety and uncertainty that their health will deteriorate in the future[8-10,13,15-17].

Antiviral treatment for chronic HCV can permanently eliminate the virus. Patients who successfully complete treatment can achieve a sustained virological response (SVR) or “viral cure” 12 weeks after treatment ends. SVR is associated in some patients with reversal of liver damage, and reductions in liver disease, liver-related death, and death due to all causes (e.g., cardiovascular, diabetes)[18-20]. In addition, SVR is associated with improvements in HRQOL and the symptom of fatigue at 3 months post-treatment[21,22]. Importantly, many other benefits that may accompany viral cure have not been evaluated.

In the last 3 years, several new DAA medications have been FDA-approved for the treatment of chronic HCV [23-26]. Other medications for the treatment of HCV are expected to be approved in 2016. Cure rates have typically been between 70% - 90% in phase III drug trials, depending on patient characteristics such as genotype and cirrhosis status[27]. Treatment lasts between 8 and 24 weeks as opposed to previous interferon-based regimens of 24 or 48 weeks. These newly-approved all-oral regimens appear much more tolerable and efficacious in phase III trials, compared to previous interferon-based regimens.

These exciting, newly-approved regimens have not been extensively evaluated, particularly with regard to issues that patients care about or longer-term harms and benefits. Differences between specific subgroups of patients have also not been evaluated. Although cure rates are relatively high and side effects fewer and less severe than prior interferon regimens, treatment side effects still exist and may be different between regimens, especially in vulnerable subgroups (e.g., those with cirrhosis, mental health or substance abuse issues). Moreover, the only treatment harms measured in previous trials were captured as clinician-reported adverse events (AEs), as opposed to patient reported. Fatigue, headache, nausea, insomnia, body weakness, diarrhea and rash were reported as AEs in >10% of participants in previous drug trials. Previous research demonstrates that clinician-reported AEs often underestimate the patients’ experience of side effects. Since most symptoms and side effects are a highly subjective, personal experience, the correlation between clinician-reported and patient-reported side effects is often quite low[28]. Finally, patients care about long-term benefits of being cured and whether symptoms associated with HCV attenuate, but few studies address these patient-centered outcomes. Therefore, outcomes chosen by, and reported by patients with the disease, are needed.

Currently, major evidence gaps exist that significantly limit our understanding of the short-term and long-term harms and benefits of these new treatments and thus, patients and clinicians ability to make informed treatment decisions. Patient-centered outcomes research (PCOR) studies are needed to ensure that patients and clinicians understand all of the short term and long-term harms and benefits of these new regimens. The only data currently

available are from phase III clinical trials, which have inherent limitations: First, clinical trials notoriously under-represent or exclude many subgroups, such as patients with cirrhosis, psychiatric and addiction conditions, so-called 'high risk' patients. Phase III trials included between 0% and 20% of patients with cirrhosis; yet, these patients have the greatest need for treatment. Over 60% of HCV patients seeking treatment in clinical practice have psychiatric or addiction issues[29,30], yet these patients are often excluded from clinical trials. Thus, clinical trials data do not represent the broad spectrum of patients seeking treatment and do not reflect what happens in real-world clinical settings[31]. Secondly, phase III clinical trials do not provide any comparison of different regimens or important patient subgroups, such as those with psychiatric or addiction histories. Third, clinical trials have focused narrowly on short-term efficacy (SVR) and AEs, but have not captured additional information that is important to patients. Fourth, the short-term harms of treatment in clinical trials have usually been captured via clinician-reported adverse events. Research in other medical populations demonstrates that clinical data under-represent the frequency and severity of side effects compared to patient-reported experiences[28]. To date, no PCOR studies have been conducted to characterize, evaluate, and compare different treatment options or patient subgroups on PROs that are of great interest to patients and stakeholders. The sparse PRO data that has been published thus far were derived from drug trials, focused only on health-related quality of life (HRQOL) and one symptom (fatigue), and did not fully evaluate nor compare treatment regimens or patient subgroups[22,32]. Finally, because clinical trials are focused on short-term efficacy and safety, they do not capture longer term benefits of cure or harms of treatment that are also extremely important for patients to consider when making decisions about treatment.

2 STUDY RATIONALE

PROP UP is a multi-site prospective observational PCOR study that will evaluate, characterize, and compare several short-term and long-term harms and benefits associated with several HCV treatment regimens. The PCOR study proposed by PROP UP is unique, powered by patients affected by HCV, and will provide novel information for patients, clinicians, and stakeholders to enhance informed decision-making about HCV treatment.

In this study, we will collect information directly from the patients via PRO surveys measuring symptoms associated with HCV, co-morbid medical conditions, side effects associated with treatment, functional status, and out of pocket costs and medication adherence during treatment. This information will allow us to better evaluate and characterize HCV symptoms that are present at baseline, symptoms that remit after viral cure, treatment side effects/toxicity associated with various treatment options, long-term harms that may be associated with treatment, and benefits associated with viral cure.

Study results will be disseminated rapidly via partnership with patient advocacy organizations and the HCV-TARGET network, as well as through traditional scholarly output. The findings from this study will be useful to patients, their families, providers, and stakeholders who are involved in decision-making about whether or not to proceed with HCV treatment, and if so, what the short-term and long-term benefits and harms of HCV treatment, may be.

3 STUDY AIMS

3.1 Specific Aims

This study is focused on characterizing several HCV treatment regimens in terms of HCV-associated symptoms, treatment side effects, medication adherence, out of pocket costs, and long-term benefits of cure and harms associated with all-oral treatments for chronic hepatitis C, as indicated by the following patient-reported outcomes (PROs) collected before, during and up to one year after HCV treatment:

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

- 1a. The Memorial Symptom Assessment Scale (MSAS) [33,34]
- 1b. Specific side effects as measured by multiple PROMIS surveys[33]

- 1c. HCV-specific functional status as measured by the HCV-PRO[34,35]
- 1d. Pre-existing medical conditions
- 1e. Cumulative out of pocket costs during treatment

Aim 2: Evaluate differences in medication adherence between patients with and without history of mental health/substance abuse (MH/SA Hx) (*see manuscript #2 below*)

- 2a. Characterize and compare the two groups (with and without MH/SA Hx) on medication adherence while accounting for treatment regimen and pill burden.
- 2b. Estimate the effects of pill burden on medication adherence in the combined sample.
- 2c. Estimate the prevalence rates of reasons for nonadherence in the combined sample.
- 2d. Estimate the effect of medication adherence on the SVR rate at 3 months post-treatment.

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

- 3a: Amelioration of HCV-associated symptoms as measured by the MSAS and PROMIS surveys
- 3b. HCV-functional status as measured by the HCV-PRO

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

- 4a. Long-term symptoms as measured with the MSAS
- 4b. Long-term side effects as measured by PROMIS surveys
- 4c. Pre-existing medical conditions
- 4d. HCV-functional status, as measured by the HCV-PRO
- 4e. Differences in 4a-4d between patients with and without cirrhosis

3.2 Auxiliary Aims

The main objective of this study is to characterize a number of benefits and harms associated with DAA treatment and viral cure as described in Aims 1-4. However, we will also take the opportunity to examine similarities and differences between the treatment regimens using causal inference methods (*see manuscripts #1 and #3 below.*)

Planned Manuscripts to Address Specific Aims 1-4		Analysis
Aim 1: Treatment Side Effects	Manuscript describing PRO changes from baseline to during treatment to characterize each regimen in terms of treatment harms such as side effects (T2/T3 data). Auxiliary analyses will compare regimens.	page 22,25-26
Aim 2: Medication Adherence	Manuscript on medication adherence will compare patients with and without history of mental health/substance abuse, characterize the effects of adherence on SVR rate, explore reasons for nonadherence, and evaluate effects of pill burden on adherence.	page 22,25-26
Aim 3: Benefits of achieving SVR	Manuscript evaluating changes from baseline to 3-months post-treatment (T4) in HCV symptoms and other PROs in patients who achieve SVR to characterize short-term benefits of cure. The main analysis will characterize change in PROs for the total sample and auxiliary analyses will explore differences between regimens.	page 23,25-26
Aim 4: Long-term Benefits/Harms	Report of long-term patient reported harms and benefits associated with HCV treatment at 1 year post-treatment. Evaluate changes in PROs from baseline to T5, and evaluate differences between patients with and without cirrhosis. Auxiliary analyses will explore differences between regimens.	page 23,25-26
PRO Psychometrics	Manuscript to evaluate the psychometric properties of several PROs (HCV-PRO, MSAS, PROMIS) in the HCV population	
Study Protocol	Manuscript describing the PROP UP study design, methodology, and protocol	
Baseline Characteristics	Manuscript describing baseline patient characteristics of the study sample, including HCV-associated symptoms, pre-existing medical conditions, and functional status.	

4 STUDY DESIGN

4.1 Observational Study Design

This is a multi-center, longitudinal prospective, observational PCOR study that will provide characterizations and comparisons in terms of specific short-term and long-term PROs during and following DAA treatment for chronic HCV. These PROs were selected after qualitative interviews with patients and significant involvement of a patient engagement group. UNC-CH (PIs: Evon, Fried, Golin) is the lead site and the Data Coordinating Center (DCC).

No drug therapy will be administered by the research team. The study does not require drawing blood, performing lab tests, biological monitoring, or conducting physical exams. This observational study is designed to assess patient experiences in "real world" settings and hence to follow the timing and procedures for patients managed in a manner consistent with the standard of care for HCV treatment. The maximum study duration is up to 20 months, depending on length of prescribed treatment regimen.

PRO evaluation and data collection will occur on 5 occasions before, during and after HCV treatment. Participants will provide responses to several PRO surveys that measure HCV symptoms, treatment side effects, functional status, medication adherence, and out of pocket costs. Participants will self-select their preferred mode of responding to surveys in the web-based data capture system: (1) via home computers, tablet or smartphone; (2) via phone interview with research staff, or (3) via computer during clinic visit with assistance of research staff (if needed). Clinical and lab data will be entered by site research coordinators at T1 baseline and at T4: 12-weeks post-treatment.

4.2 Clinical Collaborating Settings

Nine clinical liver centers in the U.S. (Table 1) most of whom are part of the HCV-TARGET research network will participate. Each site will have a designated site PI/hepatologist and Research Coordinator(s) (RC) dedicated to the study. Each site will be under the jurisdiction, and report to, their own Institutional Review Board (IRB).

Table 1: Location of Liver Centers Participating in PROP UP

Institution	Location	Principal Investigator(s)	Type of Center
Rush University	Chicago, IL	Nancy Reau, MD	Clinical
St. Louis University	St Louis, MO	Adrian Di Bisceglie, MD	Clinical
University of Florida	Gainesville, FL	David Nelson, MD	Clinical
University of Michigan	Ann Arbor, MI	Anna Lok, MD	Clinical
University of North Carolina	Chapel Hill, NC	Donna Evon, PHD Michael Fried, MD Carol Golin, MD	Clinical, Data Coordinating Center
University of Pennsylvania	Philadelphia, PA	Rajender Reddy, MD	Clinical
Virginia Commonwealth University	Richmond, VA	Richard Sterling, MD	Clinical
Yale University	New Haven, CT	Joseph Lim, MD	Clinical
UC-Davis	Davis, CA	Souvik Sarkar, MD	Clinical

4.3 Study Population

Based on >4000 patients previously enrolled in HCV-TARGET, we anticipate patients being 21 years of age and older, 62% male, 14% African-American, 6% Hispanic, and about 50% may have cirrhosis. Investigators will consent and collect baseline PRO data for approximately 1920 patients who are prescribed an all-oral, interferon-free, treatment regimen for HCV by a liver provider. Approximately 15%-20% of those consented and who complete baseline PROs (~320 patients) may not be approved by insurance payors to start HCV treatment, and thus will not qualify to participate in the longitudinal study. We will enroll 1600 patients who meet the following three enrollment criteria to participate in the longitudinal study: (1) *provide written consent; (2) complete baseline PRO surveys; and (3) take one dose of medication.*

4.3.1 Inclusion Criteria

1. Diagnosed with chronic HCV, any genotype 1-6
2. English-speaking
3. Age 21 or older
4. Medically cleared and being prescribed one of the following DAA regimens:
    a. sofosbuvir/ledipasvir (*Harvoni*®) with or without ribavirin
    b. ombitasvir/paritaprevir/ritonavir with dasabuvir (*Viekera Pak*®*), VPK*) with or without ribavirin
    c. elbasvir/grazoprevir (*Zepatier*®) with or without ribavirin
    d. daclatasvir/sofosbuvir, with or without ribavirin (*DAC/SOF*)
    e. sofosbuvir/velpatasvir (*SOF/VEL*)

4.3.2 Exclusion Criteria

1. Inability to provide written informed consent
2. Currently participating in a pharmaceutical-sponsored drug trial of hepatitis C treatment
3. Major cognitive or mental impairment
4. Unable to read or speak English
5. Unwilling or unable to complete survey questionnaires

Pregnant and breastfeeding women are not treated with antiviral medications due to teratogenic effects, and therefore will not be included in the study population.

4.3.3 Discontinuation of Subjects from Study

Subjects who are consented and complete baseline data, but who do not commence therapy within 90 days will fail to qualify for the longitudinal study. Once participants commence therapy and are officially enrolled, we do not anticipate any reason to withdraw subjects from the study after that time. If a patient commences therapy but is prematurely discontinued from therapy, he/she will be encouraged to continue in the study and complete the remaining assessments.

Participants will be discontinued from the study for the following reasons:

- If a participant withdraws informed consent verbally or in writing
- If the study is terminated by UNC (sponsor) or PCORI (funding agency)

5 REDCap DATA COLLECTION

All data collected for PROP UP will be directly entered and stored in the web-based research electronic data capture system, called REDCap. The REDCap database for PROP UP will be stored, maintained, and monitored by the PROP UP Data Coordinating Center (DCC). The REDCap system is a secure, web-based application designed to support survey and data collection for thousands of biomedical research studies. UNC has a license to host the REDCap system. Access to the PROP UP REDCap database will be carefully restricted to authorized research team members as needed to perform their job functions, pursuant to Federal

regulations. Site RCs have access only to their site study participants. Each time research staff access REDCap, a unique electronic signature (login) is required, and REDCap maintains an audit trail of all activity. Research staff who access the REDCap system for any purpose will use a unique user ID provided by the UNC DCC. These user IDs may not to be shared or reassigned to other staff. The REDCap application for this study is hosted on a secure server environment located at UNC and governed by standard University, School of Medicine, and Federal information security policies and standards.

6 RECRUITMENT

Patients who meet inclusion/exclusion criteria and have been prescribed an all-oral treatment regimen for chronic HCV at a collaborating site should be recruited to participate in PROP UP. Patients may be recruited in-person in the clinic or by phone using a site IRB-approved phone recruitment guide. If patients are recruited by phone, research staff will leave no more than 3 voicemail messages. Eligible patients who have had prescriptions written but are waiting for medications to be approved should be approached, consented, and assisted in providing baseline PRO data in REDCap. Fifteen to 20% of patients may not start HCV treatment and therefore will not qualify to participate in the longitudinal study. Therefore, patients are not considered officially enrolled until first dose of medication has been taken.

7 INFORMED CONSENT

The investigator must obtain written IRB approval of the written informed consent form and any other information that will be provided to the participants during the consent process. Only participants able to provide written informed consent will be included in this study.

As part of conducting the informed consent process with each participant, research staff must:

- Provide a written copy of the consent form prior to study participation. The language must be non-technical and easily understood. UNC will provide a template consent form which can be modified for site purposes.
- Discuss the full details of the study with the patient in a private space.
- Allow sufficient time for patients to ask questions about the study and express understanding.
- Obtain written informed consent and HIPAA waiver signed and personally dated by the patient and by the person who conducted the informed consent process.
- Write or affix label with unique subject ID# on each page of the consent form.
- Research staff will maintain a site-specific, secure master linkage list and screen-consent log of all study participants who provide consent for the study. The linkage list/consent log may include the following data consistent with local IRB: unique subject ID, name, medical record number, date of screen/consent, and reason for non-consent if patient is not consented for the study. This log serves several purposes: (1) serves as a master linkage list in case of human or data error; (2) to ensure that the site does not issue the same subject ID twice; (3) allows RCs to identify patients who were previously consented to track for treatment start date/enrollment date; and (4) allows researchers to identify proportion of patients approached vs consented and reasons for non-consent, which is recommended by the CONSORT guidelines for observational studies and PCORI Methodological Standards.

The RC must verify informed consent has taken place for the individual by uploading a signed copy of the informed consent form to the REDCap system. The RC will store the original copies in a secure location according to standard operations approved by site IRB.

8 DATA COLLECTION PROCEDURES AT CONSENT/BASELINE VISIT

8.1 Procedures for Baseline PRO Data Collection

Baseline PRO data collection needs to be collected within a 90 day window **prior** to the patient taking his/her first dose of HCV medication, allowing up to 90 days after baseline PRO assessment to start date of HCV treatment.

Informed consent and collection of baseline PRO data should occur **during the same clinic visit to the extent possible**. After written consent is obtained, the RC will open and start the web-based REDCap research record for each new study participant. A unique subject ID number will be given specific to each site.

With the research record open, the RC will gather the following information from the patient and enter into the first form in REDCap:

- Preferred modes of responding to future PRO assessments (see section 11 below)
- Email address if selects home-based computer as a possible option
- Phone numbers if selects Call Center as a possible option
- Hometown and zip code (to calculate travel/mileage for treatment cost)
- Patient-approved address to send study reimbursement

The RC will instruct the patient to respond to all items in the Baseline PRO assessment survey. The surveys should be self-administered by the patient, but with Coordinator-assistance as needed. Participant responses to PRO surveys are completely confidential; the RC is not allowed to share these data with the participant's clinical providers. Participants should be reminded before each survey assessment that their responses to surveys are confidential and not shared with their provider or placed in their medical record.

Study participants will respond to the following PRO surveys listed in Table 3:

Table 3: Baseline PRO Data Collection

PRO surveys	Items
Sociodemographic information	10
MSAS Symptom Assessment	32
PROMIS Fatigue	7
PROMIS Pain Interference	8
PROMIS Sleep Disturbance	8
PROMIS Depression	8
PROMIS Cognition Concerns	8
PROMIS Anger	5
PROMIS Anxiety	4
PROMIS Belly Pain	6
PROMIS Diarrhea	6
PROMIS Nausea/Vomiting	4
Headache Impact Test (HIT)	6
HCV-PRO health status	16
Mental health history	5
Alcohol and drug history	5
Stigma scale	8
Pre-existing medical conditions	checklist

- RC will provide patient with study information sheet and study contact information.

- RC will provide patient with Out of Pocket Cost Log and envelope for receipts and describe how to use these tools to help participants track treatment-related costs during treatment. Participants should refer to these tools when responding to PRO surveys during treatment that are related to out of pocket costs.

If the baseline PRO assessment cannot be completed during the clinic visit, with patient opt-in to receive surveys by email, site RCs can send a survey invitation to the participant's email address. Study participants can also complete the surveys with their site RC over the phone, if needed.

8.2 Procedures for Baseline Collection of Clinical and Lab Data

The RC is responsible for entering the data fields listed in Table 2 in REDCap within one week of the date of consent. The data fields will be extracted from participants' electronic medical records.

Table 2: Clinical and Laboratory Data Collection at Time of Consent	
Clinical and Lab Data	**Description**
Prescribed Treatment regimen	- sofosbuvir/ledipasvir (*Harvoni*®) with or without ribavirin - ombitasvir/paritaprevir/ritonavir with dasabuvir (*Viekera Pak*®*), VPK*) with or without ribavirin - elbasvir/grazoprevir (*Zepatier*®) with or without ribavirin - daclatasvir/sofosbuvir, with or without ribavirin (*DAC/SOF*) - sofosbuvir/velpatasvir (SOF/VEL)
Prescribed Treatment Duration	8, 12, 16, 24 weeks
HCV Genotype 1-6	Confirm genotype 1-6 with most recent lab date
HCV Viral Load	HCV RNA quantitative viral load within last 12 months IU/mL
Evidence of cirrhosis	- No evidence - Yes evidence based on source(s): Fibroscan, biopsy, ultrasound, Fibrosure blood test, clinician judgment
FibroSCAN	kPa stage and grade from Fibroscan results submitted for insurance approval
HIV status	Test conducted and HIV status
Aspartate Aminotransferase	AST IU/L within last 6 months
Alanine Aminotransferase	ALT IU/L within last 6 months
Albumin	ALB g/dL within last 6 months
Total Bilirubin	BILI mg/dL within last 6 months
Creatinine	Creatinine mg/dL within last 6 months
International Normalized Ratio	INR within last 6 months
Platelets	PLAT 10^3/uL within last 6 months
Hemoglobin	HGB g/dL within last 6 months

9 ENROLLMENT CRITERIA

(1) Patient has provided written informed consent;
(2) Patient has completed baseline PRO surveys within 90 days prior of starting treatment; and
(3) Patient has taken at least one dose of the prescribed medication regimen.

The RC will work with clinical staff to monitor when consented patients are approved for treatment. Sites should develop their own standard operating procedures to track treatment start dates of consented patients. To officially enroll a patient in the longitudinal study, the RC will confirm enrollment criteria has been met in REDCap and will complete three data fields: "Treatment Start Date", "Prescribed Treatment Regimen" and "Prescribed Treatment Duration." These data fields must be entered **within 7 days** of the patient commencing therapy so that the PRO assessment schedule is triggered to prompt patients to complete week 4 PRO assessment.

10 PRO DATA COLLECTION TIME POINTS

Study participants will respond to PRO surveys 5 time points during the study: once before treatment begins, twice during treatment, and twice after treatment:

- T1: Baseline assessment within 90 days prior to start of treatment (ideally in clinic at time of consent)
- T2: Treatment week 4 (+/- 1 week)

- T3: Late in treatment
  - During 7th-8th week of 8 week regimen
  - During the 10th -12th week of 12 week regimen
  - During the 22nd-24th week of 24 week regimen
- T4: 12 weeks after treatment ends (+/- 3 weeks)
- T5: 12 months after treatment ends (+/- 2 months post-treatment)

11 PRO DATA COLLECTION PROCESS

All PRO data will be entered directly into REDCap system by the patient, the UNC Call Center, or the site RC. The site RC will assist patients in responding to T1 baseline PRO surveys in REDCap. Site RCs are responsible for capturing all T1 data. The DCC and UNC Call Center will manage, monitor, and prompt T2-T5 PRO data collection.

T2-T5 PRO survey data can be entered directly into REDCap via 3 options: (a) the study participant through his/her home computer, tablet, smartphone, (b) the UNC Call Center staff during phone –administered surveys, or as a last resort (c) the study participant with assistance from the research staff during regular clinic visits. For patients who have access to home-based computers, tablets or smartphones, responding to surveys on their own computer should be highly encouraged. For patients with no convenient computer access, responding to survey via phone administration is second preference. Participants will consent to storage of email addresses and phone numbers in the REDCap database in order to facilitate data collection of PRO surveys via home computers or Call Center. At the baseline T1 visit, the site RC will describe how the REDCap system works, and will discuss the three data entry options below. The participant's preferred methods will be stored in the REDCap system for collection of T2-T5 assessments. Each site RC is responsible for monitoring the insurance approval status of consented patients and initiating the patient record in REDCap to initiate enrollment. This is critical to ensure adherence to the pre-determined survey schedule in REDCap, which prompts participants and/or Call Center staff to complete each patient's T2-T5 assessments.

11.1 Data entry via participant home-based computer/tablet/smartphone

The preferred mode of data entry, to the extent possible, is for patients to complete follow-up PRO surveys independently from home computers, laptops, tablets or smartphones. Patients who opt in to storing their email address and receiving their surveys by email will be sent scheduled email reminders containing a URL link for each PRO assessment period. This link is unique to this patient at this assessment. No additional verification of identity is necessary, providing the simplest possible patient experience. When the last survey at each assessment is completed, the next invitation is sent automatically at a pre-determined time and date.

11.2 Data entry via UNC Centralized Call Center phone interviews

Participants will have the second option to complete PROs via phone interview with the UNC Centralized Call Center. The DCC will prompt the UNC Call Center to contact study participants from all 9 sites for assessment periods T2-T5. The Call Center will record participant responses to survey questions directly into the REDCap system. Phone surveys are a necessary option for patients without access to computers or with low literacy levels.

11.3 Data entry via computer during regular clinic visit

As a last resort, if a study participant does not respond to PRO survey assessment via home-computer or Call Center, the DCC will contact the site RC to request completion of PRO surveys on a laptop at a regular clinic visit. Data must be collected during eligible time window for data to be valid and participant to be reimbursed. Patients who are managed in a manner consistent with the standard of care for HCV treatment will typically attend 1 or 2 treatment visits during HCV treatment, a 12-week visit to determine SVR, and many will be scheduled for annual follow-up with their liver providers. As such, PRO survey assessments T2-T5 should

coincide with these clinic visits. Participant responses to all PRO items are to be kept confidential by the RC and not shared with the patient's clinical providers.

11.4 PRO Data Assessment Time Schedule

Table 4	T1	T2	T3	T4	T5
	Baseline	**Week 4 of TX**	**Last 2 weeks of TX**	**12 weeks post-TX**	**1 year post-TX**
PROs					
Sociodemographic	X				
MSAS Symptom Assessment	X	X	X	X	X
PROMIS Fatigue	X	X	X	X	X
PROMIS Pain Interference	X	X	X	X	X
PROMIS Sleep Disturbance	X	X	X	X	X
PROMIS Depression	X	X	X	X	X
PROMIS Cognition Concerns	X	X	X	X	X
PROMIS Irritability	X	X	X	X	X
PROMIS Anxiety	X	X	X	X	X
PROMIS Belly Pain	X	X	X	X	X
PROMIS Diarrhea	X	X	X	X	X
PROMIS Nausea/Vomiting	X	X	X	X	X
Headache Impact Test (HIT)	X	X	X	X	X
HCV-PRO health/QOL	X	X	X	X	X
Voils Med Adherence		X	X		
Out of Pocket Cost		X	X	X	
Pre-existing conditions	X	X	X		X
Stigma	X				X
Mental Health Hx	X				X
Alcohol and Drug Hx	X				X

12 PARTICIPANT REIMBURSEMENT

At each PRO survey assessment, participants will respond to several questions in REDCap or by phone-administered interview with the Call Center. PRO experts suggest that a reasonable amount of time to ask participants to complete PROs is ~15-20 minutes[79]. Our HCV Patient Engagement Group (n=6) completed a paper packet of PRO surveys, yielding an average time for completion of 18 minutes (range: 15-23). The HCV-PEG unanimously agreed that response burden was not a concern.

- **$25** for completing T1 PRO baseline assessment within 90 days prior to treatment start
- **$25** for completing T2 PRO assessment at treatment week 4 (+/- 1 week)
- **$25** for completing T3 PRO assessment at end of treatment
  - During 7th-8th week of 8 week regimen
  - During 10th -12th week of 12 week regimen
  - During 22nd-24th week of 24 week regimen

- **$40** for completing T4 PRO assessment at 12 weeks after treatment ends (+/- 3 weeks)
- **$40** for completing T5 PRO assessment at 12 months after treatment ends (+/- 2 months)

UNC or subsites will reimburse subjects each time they complete survey assessments. Notification of survey completion is identifiable in the REDCap system to trigger reimbursement to be sent. UNC and the subsites can reimburse patients with checks, cash, or gift cards for the allotted amount. UNC and subsites will ensure that study participants receive reimbursement within 4 weeks of survey completion. A tracking log of subject ID, assessment time period (T1-T5), date and type of disbursement, and disbursement amount should be retained by whichever party (UNC or subsite) is responsible for subject reimbursement and maintain with internal study records.

13 CLINICAL AND LAB DATA COLLECTION AT 12 WEEKS POST-TREATMENT

Within 30 days of a participant's 12-week visit (+/- 3 weeks), the RC will extract the data listed in Table 5 from participants' medical records and accurately record the data in REDCap database.

Table 5: Clinical and Laboratory Data Collection at 12-weeks post-treatment SVR visit	
Clinical and Lab Data	**Description**
Treatment Stop Date	mm/dd/yyyy
Actual Treatment duration	8, 12, 16, 24 weeks or Other
HCV Viral Load	HCV RNA quantitative viral load or below level of quantitation
Sustained Viral Response	SVR achieved Yes/No
Aspartate Aminotransferase	AST IU/L
Alanine Aminotransferase	ALT IU/L
Total Bilirubin	BILI mg/dL
Creatinine	Creatinine mg/dL
International Normalized Ratio	INR
Platelets	PLAT 10^3/uL
Hemoglobin	HGB g/dL

14 MEASURES: PATIENT-REPORTED OUTCOMES SURVEYS

14.1 Memorial Symptom Assessment Scale (MSAS) (Aims 1a, 3a, 4a)

The MSAS is a reliable and validated 32-item instrument that will be used to measure a number of pre-existing HCV-associated symptoms, potential treatment side effects during treatment, and change in symptoms and side effects post-treatment[38,39]. The MSAS evaluates 32 prevalent symptoms or side effects that commonly occur in medical populations and during medical treatments. Patients will first indicate the presence or absence of the symptom/side effect, and if present, will rate the construct on severity, frequency and interference. An overall treatment toxicity score using all the items (referred to as TMAS) can be analyzed as well as descriptive statistics about each symptom/side effect.

14.2 PROMIS short forms (Aim 1b, 3a, 4b)

While the MSAS is capable of capturing a comprehensive set of many potential HCV-associated symptoms and toxic treatment side effects, the Patient-Reported Outcomes Measurement Information System® (PROMIS®) short forms will be used to precisely measure very specific constructs most common or salient to HCV and its treatment. The PROMIS short forms are a comprehensive set of highly reliable and validated tools that measure symptoms or treatment side effects across a wide range of chronic medical conditions. These constructs are not confounded by items measuring other symptoms or aspects of HRQOL. Each PROMIS short form includes a subset of items from a larger item bank that were the best performing items in content validity and reliability[40,41]. PROMIS raw total scores are rescaled to a standardized T-score, which has a mean of 50 and standard deviation (SD) of 10 in the US general population.

14.2.1 PROMIS short forms to measure HCV-associated symptoms

- PROMIS Fatigue -7a
- PROMIS Sleep Disturbance-8a
- PROMIS General Cognitive Concerns-8a
- PROMIS Pain Interference-8a
- PROMIS Belly/Liver Pain-6
- PROMIS Nausea/vomiting-4
- PROMIS Diarrhea-6
- PROMIS Irritability-5a
- PROMIS Depression-8a
- PROMIS Anxiety-4a

14.2.2 PROMIS short forms to measure treatment side effects

- PROMIS Fatigue -7a
- PROMIS Sleep Disturbance-8a
- PROMIS Nausea/vomiting-4
- PROMIS Diarrhea-6
- PROMIS Irritability-5a
- PROMIS Anxiety-4a

14.3 Headache Impact Test (HIT) to measure headache as a treatment side effect

Headaches are reported as adverse events in recent Phase III trials. The PROMIS measures do not include a short form to evaluate headache. We will measure headache as a side effect of treatment with the validated 6-item Headache Impact Test[42]. Participants select responses from a 5-point Likert scale ranging from "Never" to "Always." Higher scores are indicative of worse headaches and greater impact on the functioning.

14.4 HCV-PRO to measure well-being and functioning (Aim 1c, 3b, 4d)

The HCV-PRO is a newly developed survey designed to assess the well-being and functional status of patients with HCV[43,44]. It was developed in accordance with the PRO guidelines issued by the US FDA and demonstrated good reliability and convergent validity was moderate-high ($r > 0.50$) 74. HCV-PRO items measure physical, emotional and social functioning, productivity, intimacy, and perception of quality of life. Participants select responses from a 5-point Likert scale: 1="all of the time'' to 5="none of the time". A higher total score indicates higher functioning.

14.5 Out of Pocket Costs survey to measure costs of treatment reported by patients (Aim 1e)

The personal cost of undergoing HCV treatment with new all-oral treatments is unknown, may vary considerably by insurance status and coverage, and may be a key consideration during patients' decision-making. The literature describes the importance of measuring both direct and indirect costs of treatment. Patients will be asked to estimate the cost of 5 direct and 5 indirect costs associated with HCV treatment. Direct costs include: HCV medication co-pays, co-pays for prescriptions to manage side effects, over the counter remedies for side effects, doctor co-pays, blood draw copays. Indirect costs include: patient's missed work/lost hourly wages, caregiver lost wages, childcare expenses, borrowing of money, gas and mileage to/from clinic.

14.6 Voils Medication Adherence Survey (VMAS) to measure medication adherence (Aim 1f)

Medication adherence (how well patients take their medications every day as prescribed) and the reason for missed doses, may vary between treatment regimens, treatment durations and among patient subgroups. The VMAS consists of 3 items that evaluated the *extent* of adherence using a 5-point Likert scale from 1=None of the time to 5=All of the time[36,37]. The 3 items assess how often participants missed doses, skip doses, or do not take doses over the past 7 days and are averaged into a single score shown to be reliable (alpha = 0.84). A

dichotomous variable will be created to categorize patients as 100% or <100% adherent. The VMAS has undergone qualitative testing in patients with HCV on antiviral therapy and is currently being validated in a HCV population on all-oral antiviral therapy.

14.7 Sociodemographic Survey

Participants will respond to sociodemographic questions at T1 baseline to characterize the study sample and explore as confounding variables: age, sex at birth, race, marital status, educational status, income level, living situation, employment status, and health coverage.

14.8 Psychiatric and Substance Abuse History

Patients with histories of psychiatric and addiction histories are important subgroups to evaluate, as they may have different outcomes compared to patients with psychiatric and addiction history. Participants will respond to 5 questions related to psychiatric history and 5 questions related to drug and alcohol use. Psychiatric questions include use of psychiatric medications, diagnosis of mental health problems, use of mental health treatment or services, and history of psychiatric hospitalizations. Addiction questions include frequency and amount of alcohol consumption, heavy drinking, and use of nonprescription drugs and prescribed drugs[45,46].

15 STATISTICAL ANALYSIS STRATEGY

15.1 Analysis plans registered in the master protocol document

To help ensure reproducible results, these *a priori* plans specify detailed steps for the major 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 (1) use of supportive analyses of subscales as an aid for understanding and interpreting the major analysis results, (2) a role for outcome-dependent exploratory analyses for hypothesis generation / refinement, and (3) necessary descriptive graphical and tabular methods used to characterize the participants, visualize the data and examine relationships among variables.

15.2 Strategy for analysis of PRO change from baseline as a function of subgroup and/or treatment regimen

Characterization of each subgroup or treatment regimen in terms of the interval-scale PRO variables will be based on N=1600 participants. Cirrhosis is expected in approximately 50% (n=800) of the subjects. Because subgroups, such as patients with cirrhosis, may have different experiences during and after treatment, estimation and inference characterizing the treatment regimens may be subgroup-specific (e.g., in manuscript #1 and #4). In contrast, primary analysis of the benefits of viral cure (SVR) may be all-inclusive without regard to treatment regimen (e.g., manuscript #2). The general model for change from baseline for each outcome variable (e.g., Total MSAS) may condition on covariates which include *cirrhosis status*, *age*, *race*, *sex at birth, treatment regimen*, the *cirrhosis-by-regimen* interaction, and the *baseline score* (e.g., Total MSAS). The models fitted will provide parameter estimates that will be used to obtain point estimates and confidence intervals (CI) to characterize each treatment regimen and/or each subgroup. A limited number of statistical hypotheses will also be tested. For binary PRO scales or subscales, a similar strategy will rely on logistic regression model methods.

15.3 Supportive longitudinal analysis and interpretation of changes from baseline

HCV-related symptom scores will be measured longitudinally. As an aid to interpretation of the primary results, and for purposes of generating new hypotheses, auxiliary longitudinal analyses of these repeated measures may also be explored.

Any increments from Baseline (T1) during treatment (T2/T3) will represent worsening of HCV-related symptoms or commencement of new onset treatment side effects. Similarly, decrements from Treatment (T2/T3) to 12-weeks post-treatment (T4) will represent amelioration or disappearance of symptoms. For any

symptoms remaining at T4, decrements from T4 to T5 will represent further healing. Thus for each individual the longitudinal trajectories of the scores represents that individual's history of waxing and/or waning of HCV-related symptoms. Secondarily, complementary analyses of each of the 32 symptoms will be used to investigate whether side effects that begin during treatment tend to resolve and to investigate the incidence of new symptoms or side effects that appear after treatment ends.

Treatment-related side-effects scores will also be measured longitudinally. Ideally, any increment from T1 to T2/T3 will be completely reversed by a decrement from T2/T3 to T4 or T5. Thus for each individual, the longitudinal trajectories of the scores represents that individual's history of waxing and/or waning treatment-related side-effects and HCV-related symptoms. These trajectories will be summarized descriptively via estimates of occasion-specific mean levels (with confidence intervals) and in terms of patterns of the trajectories represented, for example, by the proportion of patients for whom all treatment-related side-effects disappeared by T4/T5.

15.4 Strategy for analysis of subgroup heterogeneity of treatment effects (HTE)

While a head to head drug comparison is not the primary goal of this study, we will take the opportunity to examine similarities and differences between the treatment regimens using causal inference methods (described in section 15.10). Fitted models will provide parameter estimates that will be used to obtain point estimates, confidence intervals (CI) and hypothesis tests to characterize and compare treatment regimens within each subgroup. For each outcome variable these auxiliary comparisons of regimens will include an equivalence test procedure as well as a superiority test procedure. The subgroup-specific treatment effects will be compared to evaluate evidence of HTE. For purposes of hypothesis generation and not testing, exploratory analyses of HTE for other subgroups will be performed; e.g, such as medication adherence rates among subgroups with mental health issues or drug and alcohol use (MH/SA Hx), or other groups that may be suggested by the data. Hypotheses will be generated but not tested.

15.5 Overview of Plans for Manuscript #1: Change in Treatment Side Effects from T1 to T2/T3

The primary analyses for manuscript #1 will rely on a linear model for change from baseline for each PRO variable conditional on baseline covariates which include *cirrhosis status*, *age*, *race*, *sex at birth, treatment regimen*, *cirrhosis-by-regimen* interaction, and the *baseline PRO score*. Inclusion of the baseline PRO score as a covariate has several advantages for clarity of interpretation and improved precision of estimators of interest. The analysis will focus on point estimates and confidence intervals.

PRO variables of interest in manuscript #1 are described here by aim:

Aim 1a, MSAS. The outcome variable will be change from baseline (T1) to the larger of the two MSAS scores (T2 and T3) during treatment. As an aid to interpretation, additional supportive tabulations for each of the 32 side effects will be examined; e.g., the incidence of new side effects and the exacerbation of existing symptoms during treatment will be characterized in regard to the raw frequency, severity and distress items.

Aim 1b, PROMIS®. The primary analyses will focus on 6 side effect-specific PROMIS® T-scores and 1 HIT headache score. The outcome variable will be change from baseline (T1) to the larger of the two T-scores (T2 and T3) during treatment. As an aid to interpretation of the main results, additional supportive tabulations for specific survey items will be examined.

Aim 1c, HCV-PRO. In the primary analysis, the outcome variable will be change from baseline to the larger of the two HCV-PRO scores (T2 and T3) during treatment.

Aim 1d, Pre-existing medical conditions. For each of several selected pre-existing condition at baseline, we will descriptively examine which conditions stay the same, get worse, or get better, during HCV treatment.

Aim 1e, OOP Costs. This outcome variable will be patient-reported cumulative (T2-T4) direct costs and indirect costs on $\log_{10}$ scale. Sensitivity analyses will include use of a generalized log-linear model. Treatment differences in OOP costs could affect adherence and / or persistence and hence impact SVR. The co-variation of OOP costs with other outcomes will be explored in order to generate new hypotheses about the role of OOP costs.

15.6 Overview of Plans for Manuscript #2: Medication Adherence during T1 to T2/T3

Aim 2, Medication Adherence. The analyses concerning adherence will be based on the patient-reported Voils' Medication Adherence Survey (VMAS) at 3 months post-treatment.

Aim 2a. In the combined convenience sample of 1600 participants, two subgroups defined by mental health or substance abuse history (MH/SU Hx: yes, no) will be characterized and compared in terms of medication adherence using the VMAS. We anticipate 50% (n=800) of participants having a MH/SU Hx and 50% (n=800) without a MU/SU Hx. We hypothesize that the two subpopulations are equivalent with regard to medication adherence (<5% difference in medication adherence). Each participant's level of adherence will be classified as high (100% adherent) or low (<100% adherent) for purposes of the analysis. Overall, we anticipate that about 75% of participants will report perfect 100% adherence. Individual adherence may vary depending on treatment regimen, pill burden and patient characteristics. The adherence literature suggests that adherence decreases as the number of pills in the regimen increases (Claxton). The primary characterization of each subgroup, and their comparison, we rely on a logistic regression model for adherence conditional on *subgroup, pill burden, cirrhosis status, age, race*, and *sex at birth*. The analysis will focus on point estimates and confidence intervals. In particular, the rate (P) of high adherence for each subgroup, and the magnitude of difference between those two rates, are of greatest interest. Of less interest, an equivalence test procedure will be used to test the null hypothesis that the subpopulations do not have equivalent rates. 'Equivalent' will be defined to mean that the difference between population rates, (P_1 - P_2), is less than 5%, and thus the null hypothesis is $|P_1 – P_2| > 5\%$. For purposes of generating new hypotheses, variations on the model will be explored using additional or alternative covariates such as *marital status, educational status, income level, living situation, employment status, health coverage*, and selected two-way interactions thereof.

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

Aim 2c. Descriptive analyses will also be performed investigate prevalence of various reasons patients miss taking medication (i.e., are <100%). The investigation will be based on the responses of those participants who reported imperfect adherence (n ≈ 400 = ¼ 1600). Each participant will be asked to rate 8 reasons for missing pills, based on a 5 point scale from "not at all" to "very much" We will calculate a score for each reason to determine the most common reasons for nonadherence.

Aim 2d. We will explore the relationship between medication adherence and SVR rate at 3 months post-treatment. The investigation will be based on the combined convenience sample of 1600 participants and will rely on a logistic regression model for SVR that conditions on *adherence group (100% vs < 100% adherent)* and the following covariates*: cirrhosis status, age, race*, and *sex at birth*. Variations on this model will be explored. The analysis will focus on point- and interval-estimates of the SVR rate as a function of adherence and pill burden evaluated at reference levels of the covariates.

15.7 Overview of Plans for Manuscript #3: Benefits of Achieving SVR

In the combined convenience sample of participants who achieve SVR (estimated to be ~1500), subgroups defined by achievement of SVR will be characterized and compared in terms of changes in PRO measures. The primary analyses for manuscript #3 will rely on a linear model for change from baseline for each PRO variable conditional on covariates which include *SVR status*, *cirrhosis status*, *age*, *race*, *sex at birth, treatment regimen*, *subgroup-by-regimen* interaction, *cirrhosis-by-regimen* interaction, and the *baseline PRO score*. Including the baseline PRO score as a covariate has several advantages for clarity of interpretation and improved precision of estimators of interest. The analysis will focus on point estimates and confidence intervals. PRO variables of interest in manuscript #3 are described here by aim:

Aim $3a_1$, MSAS. The outcome variable will be change from baseline (T1) to 3 months after end of treatment (T4). As an aid to interpretation, additional supportive tabulations for each of the 32 symptoms will be examined; e.g., change in side effects or pre-existing symptoms will be characterized in regard to change in raw frequency, severity and distress items.

Aim $3a_2$, PROMIS®. The primary analyses will focus on 10 symptom-specific PROMIS® T-scores and 1 HIT headache score. The outcome variable will be change from baseline (T1) to 3 months after end of treatment (T4). As an aid to interpretation of the main results, additional supportive tabulations for specific survey items will be examined.

Aim 3b, HCV-PRO. In the primary analysis, the outcome variable will be change from baseline (T1) to 3 months after end of treatment to determine benefit to well-being and functioning after cure (T4).

15.8 Overview of Plans for Manuscript #4: Long-term Benefits / Harms

The primary analyses for manuscript #4 will rely on a linear model for change from baseline(T1) to one year post treatment (T5) for each PRO variable conditional on baseline covariates which include *cirrhosis status*, *age*, *race*, *sex at birth, treatment regimen*, *cirrhosis-by-regimen* interaction, and the *baseline PRO score*. Including the baseline PRO score as a covariate has several advantages for clarity of interpretation and improved precision of estimators of interest. The analysis will focus on point estimates and confidence intervals. As an aid to interpretation of the primary results, and for purposes of generating new hypotheses, auxiliary longitudinal analyses of the repeated measures will also be explored. The PRO variables of interest in manuscript #4 are described here by aim:

Aim 4a, MSAS. The outcome variable will be change from baseline (T1 to T5) in the total MSAS score. As an aid to interpretation, additional supportive tabulations for each of the 32 side effects will be examined; e.g., change in side effects/pre-existing symptoms will be characterized in regard to the raw frequency, severity and distress items.

Aim 4b, PROMIS. The primary analyses will focus on 10 symptom-specific PROMIS® T-scores and 1 HIT headache score. The outcome variable will be change from baseline (T1 to T5) in the total score. As an aid to interpretation of the main results, additional supportive tabulations for specific survey items will be examined.

Aim 4c, Pre-existing medical conditions. For each of several patient selected pre-existing conditions at baseline, we will descriptively examine which conditions stay the same, get worse, or get better one year after treatment ends. For the primary analyses, the outcome variable will be change from baseline (T1 to T5).

Aim 4d, HCV-PRO. The outcome variable will be change from baseline (T1 to T5).

Aim 4e, Cirrhosis differences. For each regimen we will evaluate the apparent effect of cirrhosis status on change from baseline (T1 to T5) for each of the outcome variables (4a, 4b, 4c, 4d). The results will be obtained from the models fitted for Aims 4a, 4b, 4c and 4d.

Auxiliary analyses comparing treatment regimens. Although not the purpose of this study, we will also take the opportunity to examine similarities and differences between regimens. Causal inference methods (section 15.10) will be used to fit response models similar to those fitted for Aims 3a, 3b, 3c and 3d.

15.9 No Interim Analysis

Interim analyses will be conducted for two purposes: (1) To coincide with submission of abstracts to professional conferences and (2) To use portions of the earlier data as it accrues for protocol monitoring, and development and coding of statistical algorithms in SAS. Blinding to treatment condition or group will be used if deemed necessary. Interim analyses for the purpose of early treatment or study discontinuation, as a function of evidence of treatment efficacy, safety issues, or futility, will not be conducted.

15.10 Role of Causal Inference Methods

The participants will comprise two or more regimen-specific treatment cohorts. The auxiliary analyses comparing regimens will require application of causal inference methods.

Two stages of analysis. The causal inference analysis strategy comprises **(1) a design stage** involving estimation and use of a propensity score model for purposes of achieving balance of baseline covariates, and **(2) an outcomes analysis stage** for treatment effect estimation and inference separately for each outcome variable. For these two stages we may rely on the approach proposed by Cao et al.[47] building on previous work by Tan[48,49], Robins et al[50], Funk et al[51] and others. Rotnitzky et al[52] proposed a competing approach and compared the performance of their method to that of Cao et al.[47]. In the manner of Cao et al., we will use an improved doubly robust (DR) estimator obtained via enhancements in the estimation of the propensity score model and the inverse-probability weighted (IPW) outcome model. Confidence intervals will rely on bootstrap methods. Similar analytic methods will be employed to compare patient subgroups or different treatment durations.

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

Unverifiable Assumptions. All baseline variables that have a causal effect on treatment assignment and on the outcome variables must be included in the set of covariates used in the design stage. The required assumption of "no unmeasured confounders" is unverifiable. Although limited by the necessity of making additional assumptions and conjectures, efforts will be made to investigate the potential magnitude of residual bias that would exist if any unmeasured confounders exist. Additionally, if a strong instrumental variable (IV) has been identified for use in analysis of a particular outcome variable, then an auxiliary analysis will be performed using the IV approach however, the IV results would only be used to guide confidence in the main results obtained by the IPW approach and would not replace those results. The unverifiable assumption of the IV approach is that the instrument is not correlated with an unobservable error term.

15.11 Methods for Coping with Missing Data

The analysis plan relies on an extensive set of covariates measured at baseline. For purposes of estimation of the propensity score model, missing covariate values will be addressed via multiple imputation; furthermore, for each participant, the resulting multiplicity of propensity scores will be averaged together as proposed by Mitra and Reiter[53]. The alternatives (e.g., average results from multiple outcome models) will be explored for purposes of sensitivity analysis. More generally, best practices for dealing appropriately with incomplete data, especially PROs, will depend on the documented causes of the missing, censored, or coarsened values. Every effort will be made to document the causes and to avoid incomplete data by capturing the PRO data even when the participant terminates treatment earlier than scheduled. Depending on the mechanisms which cause loss-to-follow-up for outcomes such as the MSAS at 1 year, multiple imputation methods may be appropriate. Competing model-based methods will be examined for purposes of sensitivity analysis.

15.12 Overview of Sample Size Considerations

The proposed PROP UP sample size is N = 1600 participants. The rationale for this choice was based on aim-specific considerations of the availability of eligible subjects, feasible rates of recruitment, the length of time available to conduct the study, the per-subject costs in time and effort, and considerations of the anticipated levels of precision of estimators and the anticipated levels of power of statistical hypothesis tests. The 1600 participants will comprise two to five treatment cohorts. Participants receiving Harvoni® are expected to comprise about 60% of the participants (n ≈ 960), while perhaps 5% will receive Viekira Pak® (n ≈ 80)and 10% may receive Zepatier® (n ≈ 160). Other treatment cohorts may comprise 10% (n ≈ 160), or 15% (n ≈ 240) shares of the total sample size of 1600 participants. These numbers are approximations based on the current treatment landscape, and are subject to change. In each treatment cohort, subgroups of interest are expected to be about equally prevalent; for example, about 50% will have cirrhosis, and for example about 50% are expected to have a history of mental health conditions or substance abuse. In contrast, the subgroup of participants who achieve SVR is anticipated to comprise roughly 94% of the total sample size (n ≈ 1500).

Table 6. Anticipated Sample Sizes that May be Observed

	Treatment Regimen	Potential Subsample*	Potential Subsample*	Combined
Genotype 1	Harvoni® (H)	480	480	960
	Zepatier® (Z)	80	80	160
	VPK®	40	40	80
Genotype 2 & 3	Daclatasvir/sofosbuvir	40	40	80
	**Sofosbuvir/velpatasvir	60	60	120
	Combined	800	800	1600

Note: * Potential subsamples within treatment regimens may include patients with and without cirrhosis or patients with and without a mental health or substance abuse history. ** SOF/VEL is pan-genotypic and may also be used with Geno 1. Anticipated FDA-approval June 28, 2016. ***Participants with rare genotypes (4, 5, 6) are expected to represent <3% of the sample and will be analyzed based on prescribed treatment regimen, not genotype.

The primary objective of the study will focus on characterizing each treatment regimen or a subgroup of interest. For this purpose, point and interval estimates of mean changes from baseline for the PRO variables of interest will be estimated as a function of subgroups defined by cirrhosis status and other characteristics.

Auxiliary analyses to conduct head to head comparisons of treatment regimens is not the purpose of this study; however, we will take the opportunity to examine similarities and differences between regimens using causal inference methods.

Population inferences will rely on point and interval estimates, and secondarily on two kinds of tests: a 2-sided superiority test of the null hypothesis H_o: "the difference is exactly zero", and an equivalence test of the null hypothesis H_o: "the magnitude of the difference exceeds a threshold that defined 'equivalence'." Equivalence tests will be used for those analyses in which there is an *a priori* belief that equivalence is plausible; for example, in manuscript #2, it is conjectured that the subgroups of interest (patients with and without mental health/substance abuse histories) may be equivalent in regard to medication adherence.

The proposed primary hypothesis tests regarding subgroup differences or temporal changes in mean levels of outcomes will be cirrhosis-subgroup-specific; consequently, the effective sample size available to each test is approximately 800 subjects. For purposes of analysis of the anticipated levels of precision of estimators and the anticipated levels of power of test procedures, we assumed balance of covariates, inclusion of baseline score in models for change from baseline, and that the tests are those of size $\alpha = 0.05$.

Anticipated levels of precision for interval-scale estimates used to characterize change in PROs.
The appendix provides manuscript-specific details regarding the performance characteristics of the estimators and tests of interest.

- For MSAS estimators of mean change (Δ) from baseline, a change of Δ=0.10 points is considered clinically important to patients. The half-widths of the confidence intervals for mean change are highly likely (80% chance) to be < 0.14 for N=80, < 0.10 for N=160, and < 0.04 for N=960. (Appendix Figure 1-1 to Figure 1-6).
- For PROMIS estimators of mean change (Δ) from baseline, a change of Δ=3 points is considered clinically important. The half-widths of the confidence intervals for mean change are highly likely (80% chance) to be < 2.37 for N=80, < 1.63 for N=160, and < 0.65 for N=960. (Appendix Figure 2-1 to Figure 2-6).
- For HCV-PRO estimators of mean change (Δ) from baseline, a change of Δ=10 points is considered clinically important. The half-widths of the confidence intervals for mean change are highly likely (80% chance) to be <6.14 for N=80, <4.23 for N=160, and < 1.67 for N=960. (Appendix Figure 3-1 to Figure 3-6).

Anticipated levels of precision for estimates of adherence rates
For estimators of the rate of successful adherence to treatment protocol, population rates that differ by <0.05 will be considered equivalent. The half-widths of the confidence intervals for mean change are highly likely (90% chance) to be <0.09 for N=80, <0.06 for N=160, and < 0.03 for N=960. (Appendix Figure 4-1 to Figure 4-6).

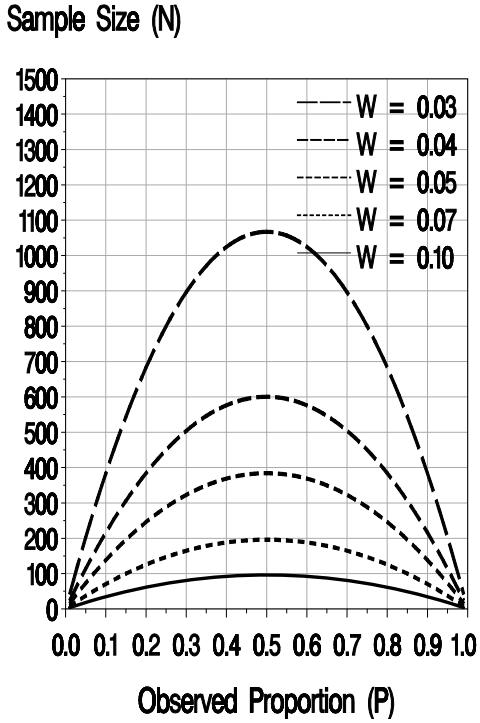
Anticipated levels of power of tests for interval scale variables to examine group differences. The appendix provides manuscript-specific details regarding the performance characteristics of the estimators and tests of interest.

- MSAS: The anticipated power level of a test of 'no difference' (Δ=0) between two subgroups each of size N=80 is 80% if Δ=0.27. For two subgroups of size N=800, anticipated power is 80% if Δ=0.08. (Appendix Figure 1-13 to Figure 1-20). The difference, Δ, is considered clinically important if $\Delta \geq 0.10$.
- PROMIS: The anticipated power level of a test of 'no difference' (Δ=0) between two subgroups each of size N=80 is 80% if Δ=4.46. For two subgroups of size N=800, anticipated power is 80% if Δ=1.40. (Appendix Figure 2-13 to Figure 2-20). The difference, Δ, is considered clinically important if $\Delta \geq 3$.
- HCV-PRO: The anticipated power level of a test of 'no difference' (Δ=0) between two subgroups each of size N=80 is 80% if Δ=11.55. For two subgroups of size N=800, anticipated power is 80% if Δ=3.63. (Appendix Figure 3-13 to Figure 3-20). The difference, Δ, is considered clinically important if $\Delta \geq 10$.

Anticipated level of power of equivalence tests for adherence rates
The anticipated power level of a test of equality between two subgroups each of size N=800 is >90% if the subgroup difference is Δ=0.0. If the magnitude of difference between subgroups is larger than 0.0, then the power level is smaller.

Anticipated precision of rates and proportions, in general

The figure below illustrates precision for rates and proportions corresponding to binary outcomes indicating, for example, presence or change of a side-effect, perfect medication adherence, and resolution of a symptom. The analyses will provide statistical estimates of the population proportion (P). The anticipated level of precision for the estimated proportion can be obtained from the figure. For example, hypothetically if N=100 and P=0.50 is the observed rate of perfect compliance for a treatment regimen, then half the width of a symmetric 95% confidence interval is W = 0.10 and thus the approximate 95% confidence interval would be 0.50 ± 0.10 or "[0.40, 0.60]. Larger sample sizes yield narrower confidence intervals.



16 STUDY CONDUCT

16.1 Ethics

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with this protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board (IRB) approval prior to initiation of the study.

All potential protocol deviations should be reported to UNC. Any serious breach to the protocol or principles of GCP in connection with the study or the protocol, which are likely to affect the physical or mental safety of study participants or the integrity of the study should be reported to UNC.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

16.2 Responsibilities within the Study

The study shall be conducted as described in this approved protocol. Investigators should not implement any deviation or change to the protocol without prior discussion with UNC.

16.3 Reports and Publications

The confidentiality of records that could identify participants within the database must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s). The data collected during this study are confidential and proprietary to UNC. Any publications or abstracts arising from the PROP UP study require approval by UNC, the study sponsor, prior to submission of a publication or presentation. Investigators who wish to use PROP UP data for secondary analyses should present initial concept sheet to Steering Committee. Steering Committee will require 2 weeks to review abstracts prior to submission to scientific conferences and 1 month to review manuscripts prior to submission to a peer-reviewed journal.

16.4 Database Retention and Archiving

Location of database and supporting documentation will be outlined in the final progress report submitted to PCORI.

The site investigators must retain all study records and source documents for at least 5 years after study completion (2023). Site investigators must contact UNC investigators prior to destroying any records associated with the PROP UP study.

17 DATA SAFETY MONITORING BOARD (DSMB)

There are minimal physical or other safety concerns associated with an observational study in which patients complete surveys. Because this study poses minimal harm and safety issues to study participants, no DSMB was established.

18 DATA AND STUDY MONITORING PLAN (DSMP)

The UNC investigators and DCC will meet weekly to review and monitor all aspects of the study: site recruitment, data completeness, data quality, protocol deviations, and any reported study-related adverse events. Regular reports will be prepared by the DCC to share with collaborating sites. Tables will show study progress by each clinical center and overall, including numbers consented, enrolled, data collected at each time point, study-related adverse events, and descriptive characteristics of the study sample.

PROP UP will utilize the secure REDCap data capture application hosted by UNC and the database will be monitored, maintained, and secured by REDCap data analysts of the DCC. REDCap has been used in over 15,360 projects with over 23,000 end users across 6 continents. REDCap is designed for interactive web-based data entry with real-time field validation. The DCC will also be responsible for database integrity checks, security (individual user logins, permissions based on need, and encrypted data transmission), and data retrieval and export. The secure server environment housing the database hardware is located within a hardened data center on the UNC campus, and is governed by standard University and School of Medicine information security guidelines. Weekly vulnerability detection scans, 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 weekly full system virus scans are performed.

19 PATIENT SAFETY AND MONITORING PLAN (PSMP)

19.1 Standard Medical Care

Site clinical hepatology teams are expected to oversee the health needs and medical treatment of patients who are enrolled in this observational study. Prior to enrolling in this study, participants will have been medically

cleared for HCV treatment by a site hepatology provider. Once HCV therapy commences, patients are managed by the site clinical team according to site standard clinical practices.

19.2 Risks of Study Participation

The psychological risks directly posed by an observational study and survey completion are judged to be minimal and rare (<1%). Patients could experience mild embarrassment when responding to questions if posed by research staff. To reduce this risk and prepare patients, the RC will remind study participants that participation is completely voluntary and that they do not have to answer questions that make them uncomfortable. RCs will also remind participants of all study procedures in place to protect the confidentiality of their data. RCs will be trained to collect PRO data in a professional, objective, nonjudgmental and supportive manner.

The risk of breach of confidentiality of patient information is judged to be minimal and rare (<1%). This risk, and all procedures to prevent it, should be discussed by the RC during the consenting process. RC will remind patients of safeguards to protect personal information and breach of confidentiality including use of private rooms, storage of hard copy documents in locked offices and/or cabinets, compliance with site information technology security recommendations, and use of a secure, encrypted database.

The social risks are judged to be minimal and rare (<1%) but could include loss of reputation or social stigma if participation in this study leads others to become aware of a patient's medical condition. The RC will discuss this risk and encourage patients to consider risk prevention, especially as related to communication with research staff via email and phone interviews.

19.3 Handling of Non-Study Related Harms or Adverse Events

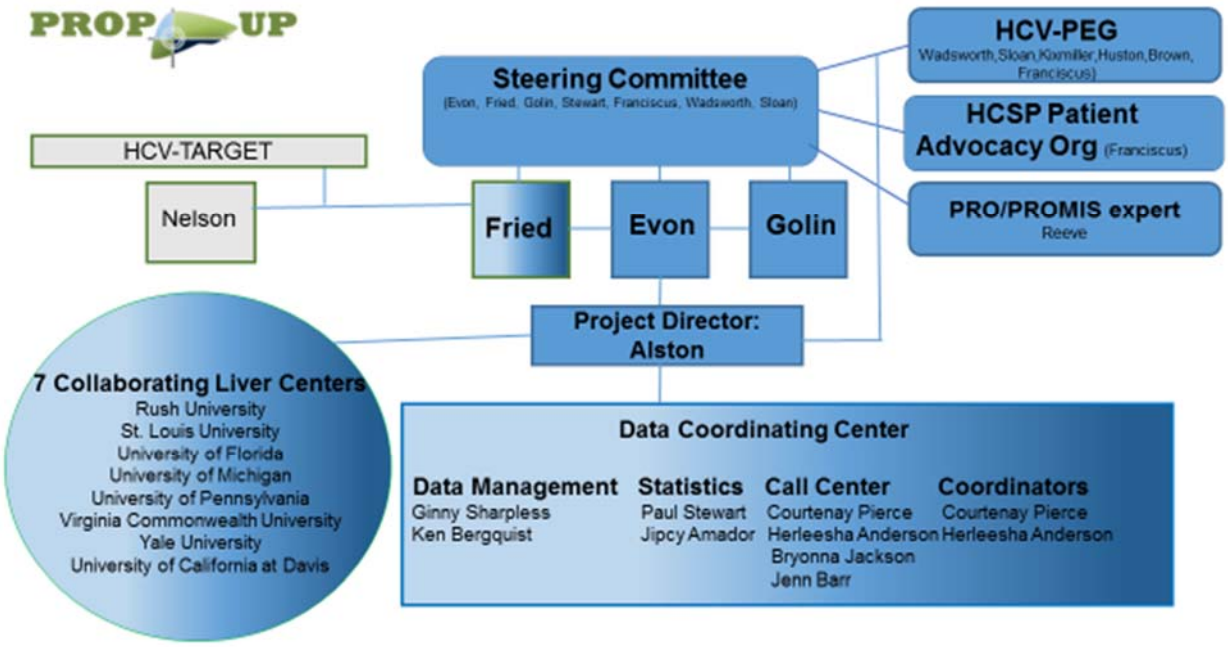
Treatment for HCV may cause side effects and adverse events related to pre-existing conditions and advanced liver disease. These harms are not considered related to study participation and are expected to be handled and managed by the site clinical providers per site standard clinical protocols for handling medical or psychiatric concerns. Non-study related harms or adverse events will not be reportable to UNC, the UNC IRB, or the sponsor.

The site research team or the UNC Call Center may become aware of a patient's medical or psychiatric concern through in-person or phone contact. The research staff will explain to the patient that research is a separate activity from clinical care and will encourage the patient to notify the clinical hepatology team at their center. In the event that a patient expresses an urgent matter or a crisis (e.g., suicidality, homicidality), the research team will be trained to use good clinical judgement and standard operating procedures (e.g., refer to liver provider, go to closest emergency room). RCs should review site standard operating procedures for handling medical and psychiatric crises.

19.4 Handling of Study-related harms or unanticipated adverse events

Harms or adverse events related to study participation in this observational survey study are expected to be extremely rare. Nonetheless, should an unanticipated study-related harm occur at a site that is judged by the site PI to be partially or fully related to study participation, the site will report this study harm to their own IRB if indicated by the site IRB standard operating procedures. Unanticipated study-related adverse events may be physical, psychological, social, or legal in nature. The site must notify UNC of the event within 10 days for study purposes. UNC will not report these events to the UNC IRB, since sites are under the jurisdiction of their own IRBs. However, overall study-related harms or unanticipated adverse events will be tracked by UNC and included in six-month progress reports to PCORI. The UNC investigators will discuss any study-related adverse events that are reported and the DCC will maintain a cumulative summary table of events, by site and date reported.

20 PROP UP RESEARCH TEAM



GLOSSARY OF TERMS AND ABBREVIATIONS

Adverse event (AE)

Agency for Health Research and Quality (AHRQ)

Center for Gastrointestinal Biology and Disease Center (CGIBD)

Clinically Important Difference (CID)

Comparative Effectiveness Research (CER)

Confidence Intervals (CI)

Consolidated Standards of Reporting (CONSORT)

Data Coordinating Center (DCC)

Data Safety Monitoring Board (DSMB)

Data and Safety Monitoring Plan (DSMP)

Doubly Robust (DR)

Food and Drug Administration (FDA)

Good Clinical Practice (GCP)

Headache Impact Test (HIT)

Health Insurance Portability and Accountability Act (HIPAA)

Health-related Quality of Life (HRQOL)

Hepatitis C Virus (HCV)

Heterogeneity of Treatment Effect (HTE)

Human Immunodeficiency Virus (HIV)

International Conference on Harmonisation (ICH)

Interferon (IFN)

Institutional Review Board (IRB)

Instrumental Variable (IV)

Inverse-probability Weighted (IPW)

Information Technology Services (ITS)

Memorial Symptom Assessment Scale (MSAS)

Patient-centered Outcomes Research (PCOR)

The Patient Centered Outcomes Research Institute (PCORI)

Patient Engagement Group (PEG)

Principal Investigator (PI)

Patient Reported Outcome (PRO)

Patient-Reported Outcomes Measurement Information System (PROMIS)

Patient-Reported Outcomes Project of HCV-TARGET (PROP-UP)

Research Electronic Data Capture system (REDCap)

Research Coordinator (RC)

Sofosbuvir (SOF)

Standard Deviation (SD)

Standard Operating Procedures (SOP)

Sustained Virological Response (SVR)

Total Memorial Symptom Assessment Scale (TMSAS)

Voils Medication Adherence Survey (VMAS)

References

1. Alter MJ. Epidemiology of hepatitis C virus infection. *World journal of gastroenterology : WJG.* 2007;13(17):2436-2441.
2. Deuffic-Burban S, Poynard T, Sulkowski MS, Wong JB. Estimating the future health burden of chronic hepatitis C and human immunodeficiency virus infections in the United States. *J Viral Hepat.* 2007;14(2):107-115.
3. Wong JB, McQuillan GM, McHutchison JG, Poynard T. Estimating future hepatitis C morbidity, mortality, and costs in the United States. *Am.J.Public Health.* 2000;90(10):1562-1569.
4. Ghany MG, Strader DB, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology.* 2009;49(4):1335-1374.
5. Ghany MG, Perrillo R, Li R, et al. Characteristics of Adults in the Hepatitis B Research Network in North America Reflect Their Country of Origin and Hepatitis B Virus Genotype. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2014.
6. Davis GL, Alter MJ, El-Serag H, Poynard T, Jennings LW. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology.* 2010;138(2):513-521, 521 e511-516.
7. Kleinman L, Mannix S, Yuan Y, Kummer S, L'Italien G, Revicki D. Review of patient-reported outcome measures in chronic hepatitis C. *Health Qual.Life Outcomes.* 2012;10:92. doi: 10.1186/1477-7525-10-92.:92-10.
8. Kallman J, O'Neil MM, Larive B, Boparai N, Calabrese L, Younossi ZM. Fatigue and health-related quality of life (HRQL) in chronic hepatitis C virus infection. *Dig.Dis.Sci.* 2007;52(10):2531-2539.
9. Lang CA, Conrad S, Garrett L, et al. Symptom prevalence and clustering of symptoms in people living with chronic hepatitis C infection. *J.Pain Symptom.Manage.* 2006;31(4):335-344.
10. Younossi Z, Kallman J, Kincaid J. The effects of HCV infection and management on health-related quality of life. *Hepatology.* 2007;45(3):806-816.
11. Basseri B, Yamini D, Chee G, Enayati PD, Tran T, Poordad F. Comorbidities associated with the increasing burden of hepatitis C infection. *Liver international : official journal of the International Association for the Study of the Liver.* 2010;30(7):1012-1018.
12. Carlson MD, Hilsabeck RC, Barakat F, Perry W. Role of Sleep Disturbance in Chronic Hepatitis C Infection. *Curr Hepat Rep.* 2010;9(1):25-29.
13. Foster GR, Goldin RD, Thomas HC. Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. *Hepatology.* 1998;27(1):209-212.
14. Spiegel BM, Younossi ZM, Hays RD, Revicki D, Robbins S, Kanwal F. Impact of hepatitis C on health related quality of life: a systematic review and quantitative assessment. *Hepatology.* 2005;41(4):790-800.
15. Zickmund S, Ho EY, Masuda M, Ippolito L, LaBrecque DR. 'They Treated Me Like a Leper': Stigmatization and the Qualify of Life of Patients with Hepatitis C. *Journal of General Internal Medicine.* 2003;18(10):835-844.
16. Fletcher NF, McKeating JA. Hepatitis C virus and the brain. *J Viral Hepat.* 2012;19(5):301-306.
17. Grover VP, Pavese N, Koh SB, et al. Cerebral microglial activation in patients with hepatitis C: in vivo evidence of neuroinflammation. *J Viral Hepat.* 2012;19(2):e89-96.
18. Backus LI, Boothroyd DB, Phillips BR, Belperio P, Halloran J, Mole LA. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association.* 2011;9(6):509-516 e501.
19. Cardoso AC, Moucari R, Figueiredo-Mendes C, et al. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. *Journal of hepatology.* 2010;52(5):652-657.
20. El-Kamary SS, Jhaveri R, Shardell MD. All-cause, liver-related, and non-liver-related mortality among HCV-infected individuals in the general US population. *Clin.Infect.Dis.* 2011;53(2):150-157.
21. Sarkar S, Jiang Z, Evon DM, Wahed AS, Hoofnagle JH. Fatigue before, during and after antiviral therapy of chronic hepatitis C: results from the Virahep-C study. *J.Hepatol.* 2012;57(5):946-952.
22. Younossi ZM, Stepanova M, Henry L, et al. Effects of Sofosbuvir-based Treatment, With and Without Interferon, on Outcome and Productivity of Patients With Chronic Hepatitis C. *Clin.Gastroenterol.Hepatol.* 2013.
23. Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med.* 2014;370(16):1483-1493.
24. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med.* 2014;370(20):1879-1888.
25. Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. *N Engl J Med.* 2014;370(21):1983-1992.

26. Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. *N Engl J Med.* 2014;370(17):1594-1603.
27. Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. *N Engl J Med.* 2014;370(21):1973-1982.
28. Basch E. The missing voice of patients in drug-safety reporting. *N Engl J Med.* 2010;362(10):865-869.
29. Evon DM, Verma A, Dougherty KA, et al. High deferral rates and poorer treatment outcomes for HCV patients with psychiatric and substance use comorbidities. *Digest Dis Sci.* 2007;52(11):3251-3258.
30. El-Serag HB, Kunik M, Richardson P, Rabeneck L. Psychiatric disorders among veterans with hepatitis C infection. *Gastroenterology.* 2002;123(2):476-482.
31. El-Serag HB, Talwalkar J, Kim WR. Efficacy, effectiveness, and comparative effectiveness in liver disease. *Hepatology.* 2010;52(2):403-407.
32. Younossi ZM, Stepanova M, Zeuzem S, et al. Patient-reported outcomes assessment in chronic hepatitis C treated with sofosbuvir and ribavirin: The VALENCE study. *Journal of hepatology.* 2014;61(2):228-234.
33. Cella D, Yount S, Rothrock N, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH Roadmap cooperative group during its first two years. *Med Care.* 2007;45(5 Suppl 1):S3-s11.
34. Anderson RT, Baran RW, Dietz B, Kallwitz E, Erickson P, Revicki DA. Development and initial psychometric evaluation of the hepatitis C virus-patient-reported outcomes (HCV-PRO) instrument. *Qual.Life Res.* 2013.
35. Anderson RT, Baran RW, Erickson P, Revicki DA, Dietz B, Gooch K. Psychometric evaluation of the hepatitis C virus patient-reported outcomes (HCV-PRO) instrument: validity, responsiveness, and identification of the minimally important difference in a phase 2 clinical trial. *Qual.Life Res.* 2013.
36. Voils CI, King HA, Neelon B, et al. Characterizing weekly self-reported antihypertensive medication nonadherence across repeated occasions. *Patient preference and adherence.* 2014;8:643-650.
37. Voils CI, Maciejewski ML, Hoyle RH, et al. Initial validation of a self-report measure of the extent of and reasons for medication nonadherence. *Med Care.* 2012;50(12):1013-1019.
38. Portenoy RK, Thaler HT, Kornblith AB, et al. The Memorial Symptom Assessment Scale: an instrument for the evaluation of symptom prevalence, characteristics and distress. *European journal of cancer (Oxford, England : 1990).* 1994;30a(9):1326-1336.
39. Chang VT, Hwang SS, Thaler HT, Kasimis BS, Portenoy RK. Memorial symptom assessment scale. *Expert review of pharmacoeconomics & outcomes research.* 2004;4(2):171-178.
40. Cella D, Riley W, Stone A, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. *Journal of clinical epidemiology.* 2010;63(11):1179-1194.
41. Reeve BB, Hays RD, Bjorner JB, et al. Psychometric evaluation and calibration of health-related quality of life item banks: plans for the Patient-Reported Outcomes Measurement Information System (PROMIS). *Med.Care.* 2007;45(5 Suppl 1):S22-S31.
42. Kosinski M, Bayliss MS, Bjorner JB, et al. A six-item short-form survey for measuring headache impact: the HIT-6. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2003;12(8):963-974.
43. Anderson RT, Baran RW, Dietz B, Kallwitz E, Erickson P, Revicki DA. Development and initial psychometric evaluation of the hepatitis C virus-patient-reported outcomes (HCV-PRO) instrument. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2014;23(2):561-570.
44. Anderson RT, Baran RW, Erickson P, Revicki DA, Dietz B, Gooch K. Psychometric evaluation of the hepatitis C virus patient-reported outcomes (HCV-PRO) instrument: validity, responsiveness, and identification of the minimally important difference in a phase 2 clinical trial. *Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation.* 2014;23(3):877-886.
45. Saunders JB, Aasland OG, Babor TF, de lF, Jr., Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. *Addiction.* 1993;88(6):791-804.
46. Pence BW, Gaynes BN, Whetten K, Eron JJ, Jr., Ryder RW, Miller WC. Validation of a brief screening instrument for substance abuse and mental illness in HIV-positive patients. *J.Acquir.Immune.Defic.Syndr.* 2005;40(4):434-444.
47. Cao W, Tsiatis AA, Davidian M. Improving efficiency and robustness of the doubly robust estimator for a population mean with incomplete data. *Biometrika.* 2009;96(3):723-734.
48. Tan Z. A Distributional Approach for Causal Inference Using Propensity Scores. *Journal of the American Statistical Association.* 2006;101(476):1619-1637.
49. Tan Z. Comment: Understanding OR, PS and DR. 2007:560-568.

50. Robins J, Sued M, Lei-Gomez Q, Rotnitzky A. Comment: Performance of Double-Robust Estimators When "Inverse Probability" Weights Are Highly Variable. *Statistical Science.* 2007;22(4):544-559.
51. Funk MJ, Westreich D, Wiesen C, Sturmer T, Brookhart MA, Davidian M. Doubly robust estimation of causal effects. *American journal of epidemiology.* 2011;173(7):761-767.
52. Rotnitzky A, Lei Q, Sued M, Robins JM. Improved double-robust estimation in missing data and causal inference models. *Biometrika.* 2012;99(2):439-456.
53. Mitra R, Reiter JP. A comparison of two methods of estimating propensity scores after multiple imputation. (1477-0334 (Electronic)).

Appendix for Sample Size Analyses

Table of Contents

1. Anticipated Sample Sizes that May be Observed

Anticipated Sample Sizes that May be Observed

	Treatment Regimen	Cirrhotic	non-Cirrhotic	Combined
Genotype 1	Harvoni	480	480	960
	Zepatier	80	80	160
	Viekira Pak	40	40	80
Genotype 2 & 3	daclatasvir/sofosbuvir	40	40	80
	sofosbuvir/velpatasvir**	60	60	120
	Combined	800	800	1600

Note: * Potential subsamples within treatment regimens may include patients with and without cirrhosis or patients with and without a mental health or substance abuse history. ** SOF/VEL is pan-genotypic and may also be used with genotype 1 patients. Anticipated FDA approval: June 28, 2016 .

2. Tabular Summary of Performance Curve Figures

PRO_measure = MSAS **with Conjectures = { SD = 0.6 [0.45, 0.75] and serial correlation is R = 0.50 }**

a difference of 0.10 points on the MSAS scale will be considered clinically important

Figure	MS	Groups	N	procedure	X_80		X_90	
1-1	1, 3, 4	1	1500	Confidence interval [1]	0.03	[0.02,0.04]	0.03	[0.02,0.04]
1-2	1, 3, 4	1	960	Confidence interval [1]	0.04	[0.03,0.05]	0.04	[0.03,0.05]
1-3	1, 3, 4	1	160	Confidence interval [1]	0.10	[0.07,0.12]	0.10	[0.08,0.13]
1-4	1, 3, 4	1	120	Confidence interval [1]	0.11	[0.09,0.14]	0.12	[0.09,0.15]
1-5	1, 3, 4	1	100	Confidence interval [1]	0.13	[0.09,0.16]	0.13	[0.10,0.16]
1-6	1, 3, 4	1	80	Confidence interval [1]	0.14	[0.11,0.18]	0.15	[0.11,0.18]
1-7	1, 3, 4	1	1500	test Ho: 'mean change is zero' [2]	0.04	[0.03,0.05]	0.05	[0.04,0.06]
1-8	1, 3, 4	1	960	test Ho: 'mean change is zero' [2]	0.05	[0.04,0.07]	0.06	[0.05,0.08]
1-9	1, 3, 4	1	160	test Ho: 'mean change is zero' [2]	0.13	[0.10,0.17]	0.15	[0.12,0.19]
1-10	1, 3, 4	1	120	test Ho: 'mean change is zero' [2]	0.15	[0.12,0.19]	0.18	[0.13,0.22]
1-11	1, 3, 4	1	100	test Ho: 'mean change is zero' [2]	0.17	[0.13,0.21]	0.20	[0.15,0.25]
1-12	1, 3, 4	1	80	test Ho: 'mean change is zero' [2]	0.19	[0.14,0.24]	0.22	[0.17,0.28]
1-13	1, 3A, 4	2	800 + 800	test Ho: 'mean diff. is zero' [3]	0.08	[0.06,0.11]	0.10	[0.07,0.12]
1-14	1, 3A, 4	2	1500 + 100	test Ho: 'mean diff. is zero' [3]	0.18	[0.13,0.22]	0.20	[0.15,0.25]
1-15	1, 3A, 4	2	400 + 400	test Ho: 'mean diff. is zero' [3]	0.12	[0.09,0.15]	0.14	[0.10,0.17]
1-16	1, 3A, 4	2	160 + 120	test Ho: 'mean diff. is zero' [3]	0.20	[0.15,0.25]	0.24	[0.18,0.29]
1-17	1, 3A, 4	2	160 + 80	test Ho: 'mean diff. is zero' [3]	0.23	[0.17,0.29]	0.27	[0.20,0.33]
1-18	1, 3A, 4	2	80 + 80	test Ho: 'mean diff. is zero' [3]	0.27	[0.20,0.33]	0.31	[0.23,0.39]
1-19	1, 3A, 4	2	960 + 80	test Ho: 'mean diff. is zero' [3]	0.20	[0.15,0.25]	0.23	[0.17,0.29]
1-20	1, 3A, 4	2	960 + 160	test Ho: 'mean diff. is zero' [3]	0.14	[0.11,0.18]	0.17	[0.13,0.21]

[1] Pr[Confidence Interval's half-width will be < X_80] = 0.80
[2] Pr[p < alpha | population mean change = X_80] = 0.80
[3] Pr[p < alpha | population mean difference = X_80] = 0.80
[4] Pr[p < alpha | population rate change = X_80] = 0.80
[5] Pr[p < alpha | population rate difference = X_80] = 0.80

PRO_measure = PROMIS with Conjectures = { SD = 10 [6, 12] and serial correlation is R = 0.50 }

a difference of 3 points on a PROMIS scale will be considered clinically important

Figure	MS	Groups	N	procedure	X_80		X_90	
2-1	1, 3, 4	1	1500	Confidence interval [1]	0.52	[0.31,0.62]	0.52	[0.31,0.63]
2-2	1, 3, 4	1	960	Confidence interval [1]	0.65	[0.40,0.78]	0.66	[0.41,0.79]
2-3	1, 3, 4	1	160	Confidence interval [1]	1.63	[0.98,1.96]	1.67	[1.01,2.01]
2-4	1, 3, 4	1	120	Confidence interval [1]	1.90	[1.14,2.29]	1.96	[1.18,2.35]
2-5	1, 3, 4	1	100	Confidence interval [1]	2.10	[1.26,2.52]	2.16	[1.30,2.60]
2-6	1, 3, 4	1	80	Confidence interval [1]	2.37	[1.42,2.84]	2.45	[1.47,2.94]
2-7	1, 3, 4	1	1500	test Ho: 'mean change is zero' [2]	0.72	[0.44,0.87]	0.84	[0.50,1.01]
2-8	1, 3, 4	1	960	test Ho: 'mean change is zero' [2]	0.91	[0.54,1.09]	1.05	[0.63,1.26]
2-9	1, 3, 4	1	160	test Ho: 'mean change is zero' [2]	2.23	[1.34,2.67]	2.58	[1.55,3.09]
2-10	1, 3, 4	1	120	test Ho: 'mean change is zero' [2]	2.58	[1.55,3.09]	2.98	[1.79,3.58]
2-11	1, 3, 4	1	100	test Ho: 'mean change is zero' [2]	2.83	[1.70,3.39]	3.27	[1.96,3.93]
2-12	1, 3, 4	1	80	test Ho: 'mean change is zero' [2]	3.17	[1.90,3.81]	3.67	[2.20,4.40]
2-13	1, 3A, 4	2	800 + 800	test Ho: 'mean diff. is zero' [3]	1.40	[0.84,1.68]	1.62	[0.97,1.95]
2-14	1, 3A, 4	2	1500 + 100	test Ho: 'mean diff. is zero' [3]	2.92	[1.75,3.50]	3.38	[2.03,4.05]
2-15	1, 3A, 4	2	400 + 400	test Ho: 'mean diff. is zero' [3]	1.98	[1.19,2.38]	2.29	[1.38,2.75]
2-16	1, 3A, 4	2	160 + 120	test Ho: 'mean diff. is zero' [3]	3.40	[2.04,4.08]	3.93	[2.36,4.72]
2-17	1, 3A, 4	2	160 + 80	test Ho: 'mean diff. is zero' [3]	3.86	[2.32,4.63]	4.47	[2.68,5.36]
2-18	1, 3A, 4	2	80 + 80	test Ho: 'mean diff. is zero' [3]	4.46	[2.67,5.35]	5.16	[3.09,6.19]
2-19	1, 3A, 4	2	960 + 80	test Ho: 'mean diff. is zero' [3]	3.29	[1.98,3.95]	3.81	[2.29,4.57]
2-20	1, 3A, 4	2	960 + 160	test Ho: 'mean diff. is zero' [3]	2.40	[1.44,2.88]	2.78	[1.67,3.34]

[1] Pr[Confidence Interval's half-width will be < X_80] = 0.80
[2] Pr[p < alpha | population mean change = X_80] = 0.80
[3] Pr[p < alpha | population mean difference = X_80] = 0.80
[4] Pr[p < alpha | population rate change = X_80] = 0.80
[5] Pr[p < alpha | population rate difference = X_80] = 0.80

PRO_measure = HCV-PRO with Conjectures = { SD = 25.92 [23.641, 28.835] and serial correlation is R = 0.50 }

a difference of 10 points on the HCV-PRO scale will be considered clinically important

Figure	MS	Groups	N	procedure	X_80		X_90	
3-1	1, 3, 4	1	1500	Confidence interval [1]	1.34	[1.24,1.50]	1.35	[1.26,1.51]
3-2	1, 3, 4	1	960	Confidence interval [1]	1.67	[1.54,1.88]	1.71	[1.57,1.90]
3-3	1, 3, 4	1	160	Confidence interval [1]	4.23	[3.86,4.71]	4.34	[3.96,4.83]
3-4	1, 3, 4	1	120	Confidence interval [1]	4.94	[4.50,5.49]	5.07	[4.63,5.64]
3-5	1, 3, 4	1	100	Confidence interval [1]	5.44	[4.96,6.05]	5.61	[5.11,6.24]
3-6	1, 3, 4	1	80	Confidence interval [1]	6.14	[5.60,6.83]	6.35	[5.79,7.06]
3-7	1, 3, 4	1	1500	test Ho: 'mean change is zero' [2]	1.88	[1.71,2.09]	2.17	[1.98,2.42]
3-8	1, 3, 4	1	960	test Ho: 'mean change is zero' [2]	2.35	[2.14,2.61]	2.71	[2.48,3.02]
3-9	1, 3, 4	1	160	test Ho: 'mean change is zero' [2]	5.78	[5.27,6.42]	6.68	[6.10,7.43]
3-10	1, 3, 4	1	120	test Ho: 'mean change is zero' [2]	6.68	[6.10,7.43]	7.73	[7.05,8.60]
3-11	1, 3, 4	1	100	test Ho: 'mean change is zero' [2]	7.33	[6.69,8.16]	8.48	[7.74,9.44]
3-12	1, 3, 4	1	80	test Ho: 'mean change is zero' [2]	8.22	[7.50,9.14]	9.51	[8.67,10.58]
3-13	1, 3A, 4	2	800 + 800	test Ho: 'mean diff. is zero' [3]	3.63	[3.31,4.04]	4.20	[3.83,4.68]
3-14	1, 3A, 4	2	1500 + 100	test Ho: 'mean diff. is zero' [3]	7.56	[6.90,8.41]	8.75	[7.98,9.74]
3-15	1, 3A, 4	2	400 + 400	test Ho: 'mean diff. is zero' [3]	5.14	[4.69,5.72]	5.95	[5.43,6.62]
3-16	1, 3A, 4	2	160 + 120	test Ho: 'mean diff. is zero' [3]	8.80	[8.03,9.79]	10.19	[9.29,11.33]
3-17	1, 3A, 4	2	160 + 80	test Ho: 'mean diff. is zero' [3]	10.00	[9.12,11.13]	11.58	[10.56,12.88]
3-18	1, 3A, 4	2	80 + 80	test Ho: 'mean diff. is zero' [3]	11.55	[10.54,12.85]	13.37	[12.19,14.87]
3-19	1, 3A, 4	2	960 + 80	test Ho: 'mean diff. is zero' [3]	8.54	[7.79,9.50]	9.88	[9.01,10.99]
3-20	1, 3A, 4	2	960 + 160	test Ho: 'mean diff. is zero' [3]	6.23	[5.68,6.93]	7.21	[6.57,8.02]

[1] Pr[Confidence Interval's half-width will be < X_80] = 0.80
[2] Pr[p < alpha | population mean change = X_80] = 0.80
[3] Pr[p < alpha | population mean difference = X_80] = 0.80
[4] Pr[p < alpha | population rate change = X_80] = 0.80
[5] Pr[p < alpha | population rate difference = X_80] = 0.80

PRO_measure = ADHERENCE **with Conjectures = { rate P_1 = 0.80 [0.60, 0.90] }**

population rates that differ by less than 0.05 will be considered equivalent

Figure	MS	Groups	N	procedure	X_80	X_90
4-1	1, 2	1	1500	Confidence interval [1]	0.02 [0.03,0.02]	0.02 [0.03,0.02]
4-2	1, 2	1	960	Confidence interval [1]	0.03 [0.03,0.02]	0.03 [0.03,0.02]
4-3	1, 2	1	160	Confidence interval [1]	0.06 [0.08,0.05]	0.07 [0.08,0.05]
4-4	1, 2	1	120	Confidence interval [1]	0.07 [0.09,0.06]	0.08 [0.09,0.06]
4-5	1, 2	1	100	Confidence interval [1]	0.08 [0.10,0.07]	0.08 [0.10,0.07]
4-6	1, 2	1	80	Confidence interval [1]	0.09 [0.11,0.07]	0.09 [0.11,0.08]
4-7	1, 2, 3A	2	800 + 800	test Ho: 'rate difference is zero' [5]	0.06 [0.07,0.05]	0.07 [0.08,0.05]
4-8	1, 2, 3A	2	800 + 800	test Ho: 'rates are equivalent(0.05)' [5]	0.00 [0.00,0.00]	0.00 [0.00,0.00]

[1] Pr[Confidence Interval's half-width will be < X_80] = 0.80
[2] Pr[p < alpha | population mean change = X_80] = 0.80
[3] Pr[p < alpha | population mean difference = X_80] = 0.80
[4] Pr[p < alpha | population rate change = X_80] = 0.80
[5] Pr[p < alpha | population rate difference = X_80] = 0.80

3. Performance Curve Figures: Anticipated Precision of Estimators and Anticipated Power of Tests

Figure 1-1 MSAS

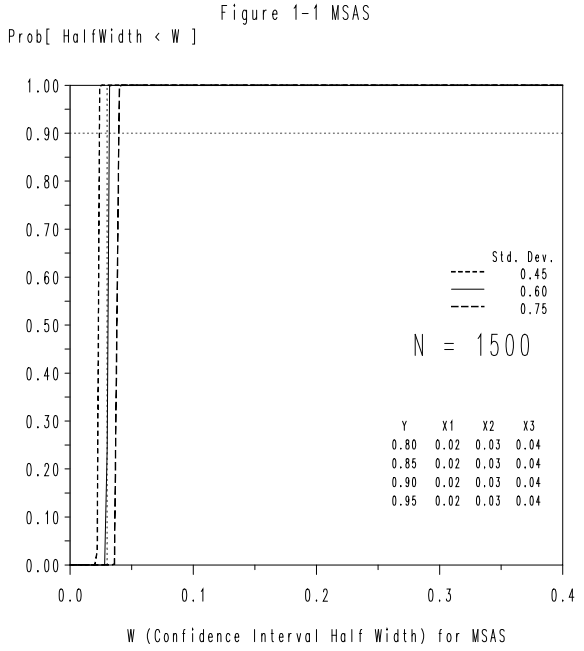


Figure 1-2 MSAS

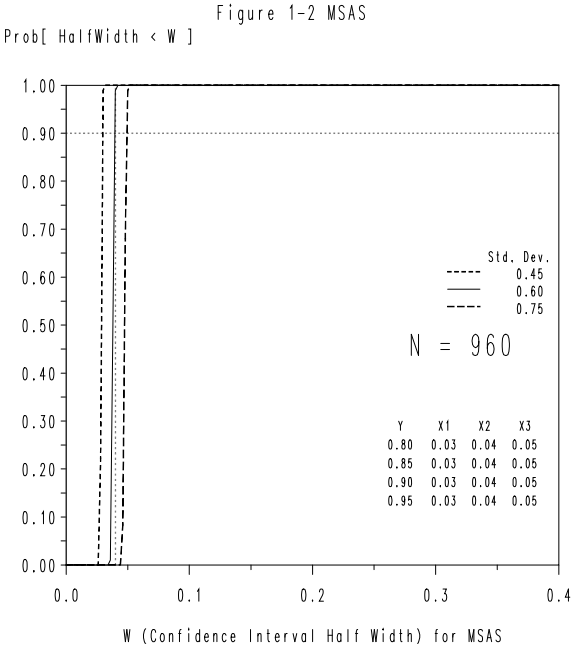


Figure 1-3 MSAS

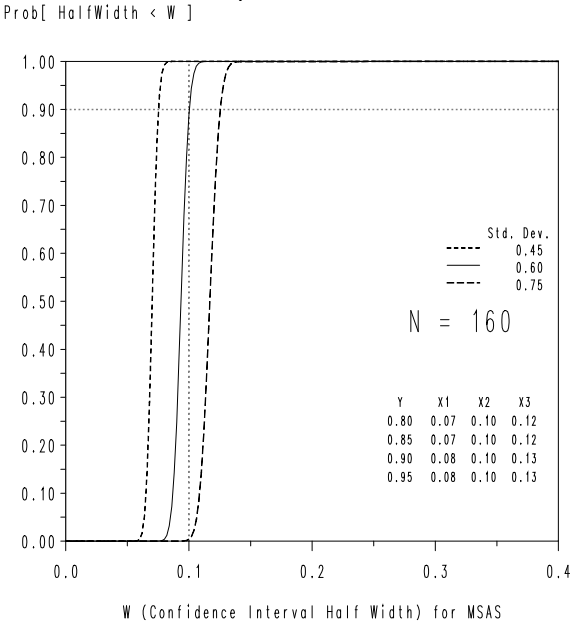


Figure 1-4 MSAS

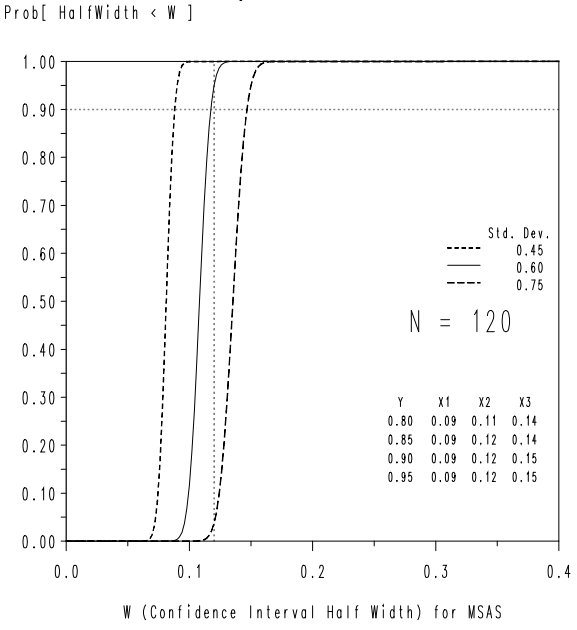


Figure 1-5 MSAS

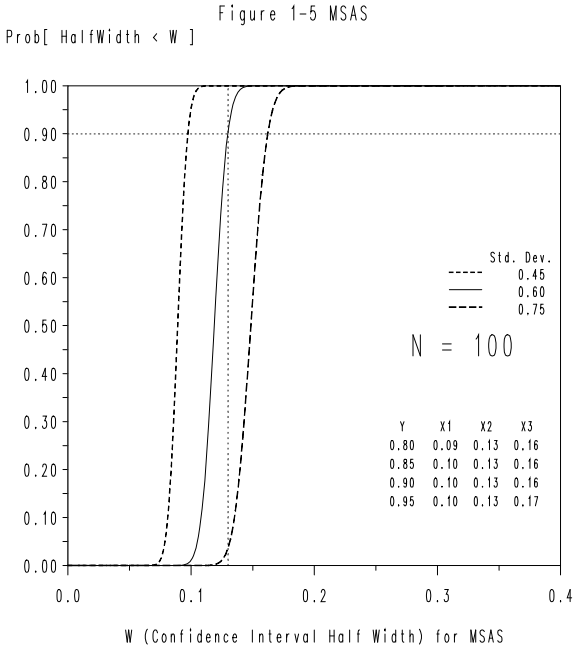


Figure 1-6 MSAS

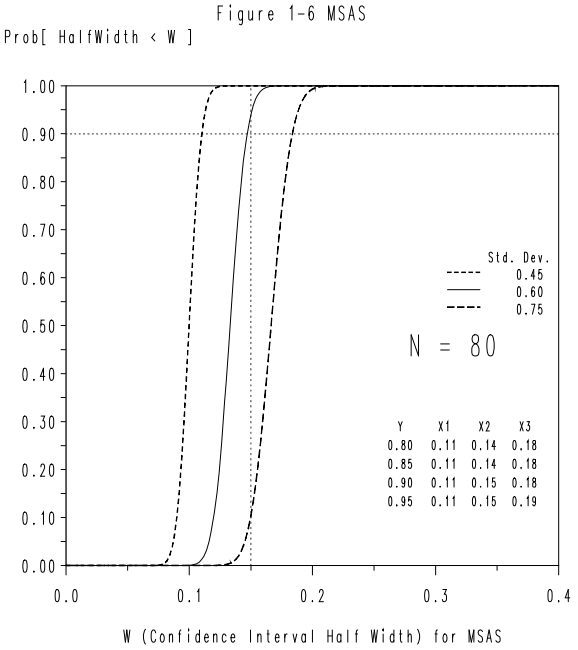


Figure 1-7 MSAS

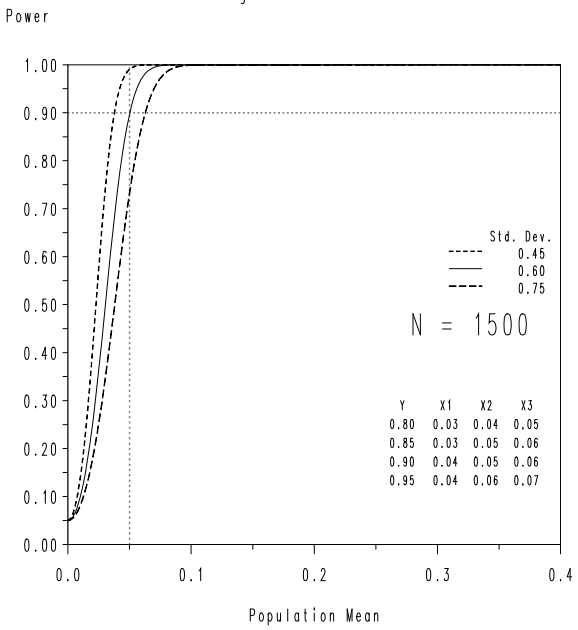


Figure 1-8 MSAS

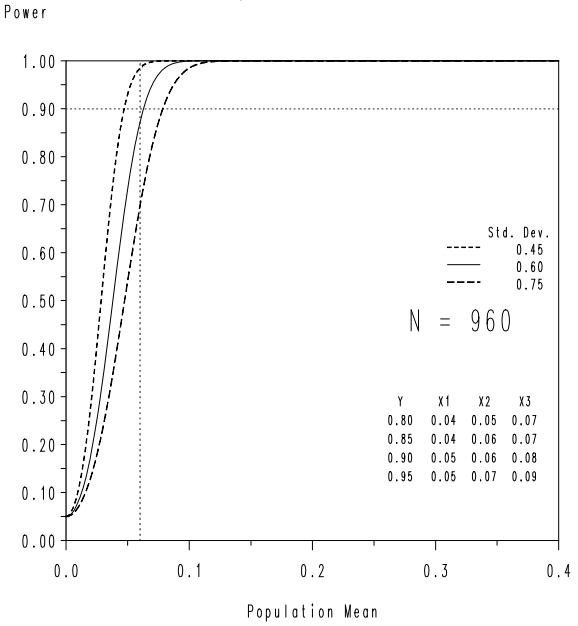


Figure 1-9 MSAS

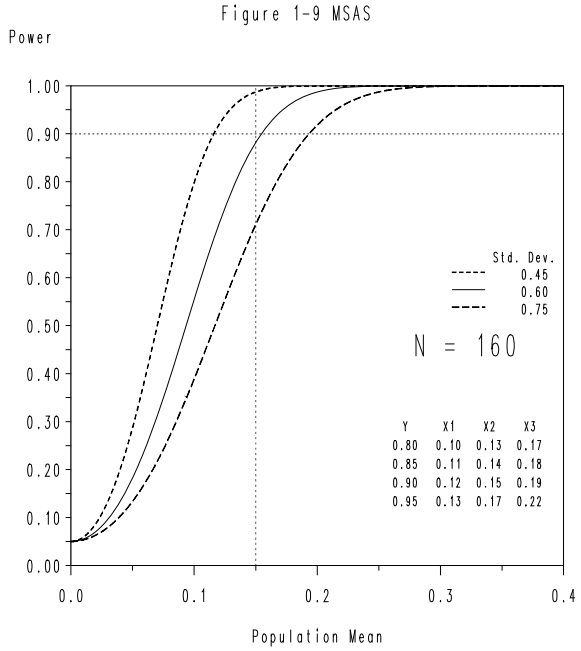


Figure 1-10 MSAS

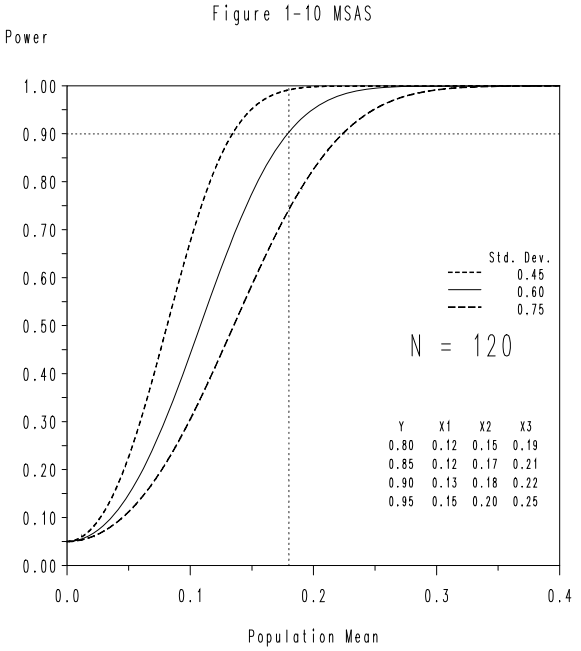


Figure 1-11 MSAS

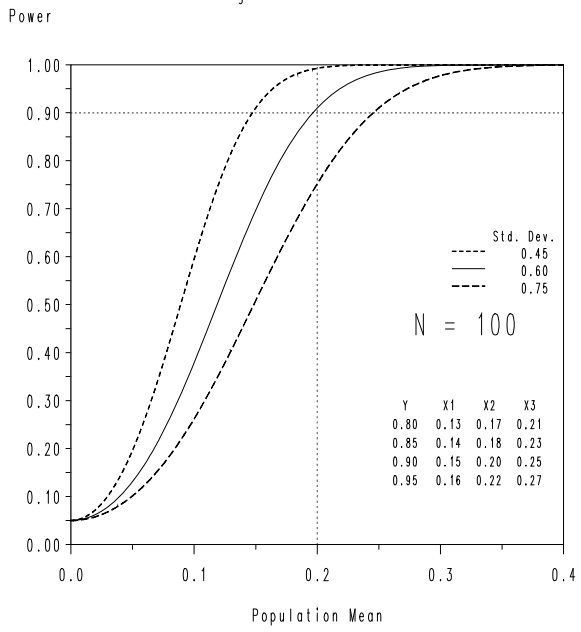


Figure 1-12 MSAS

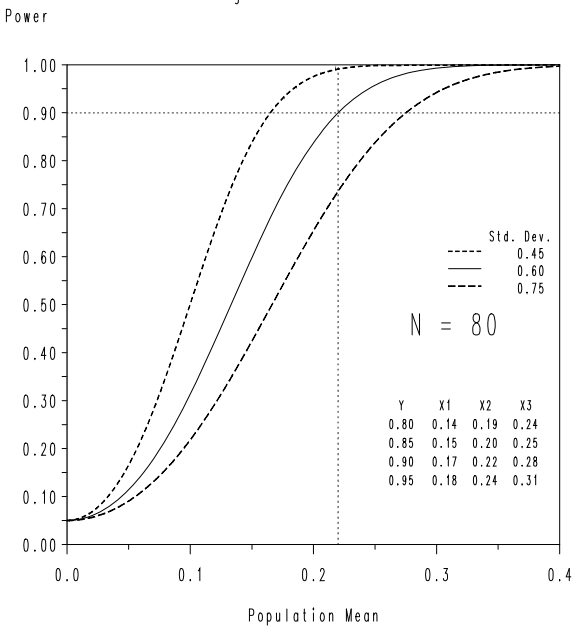


Figure 1-13 MSAS

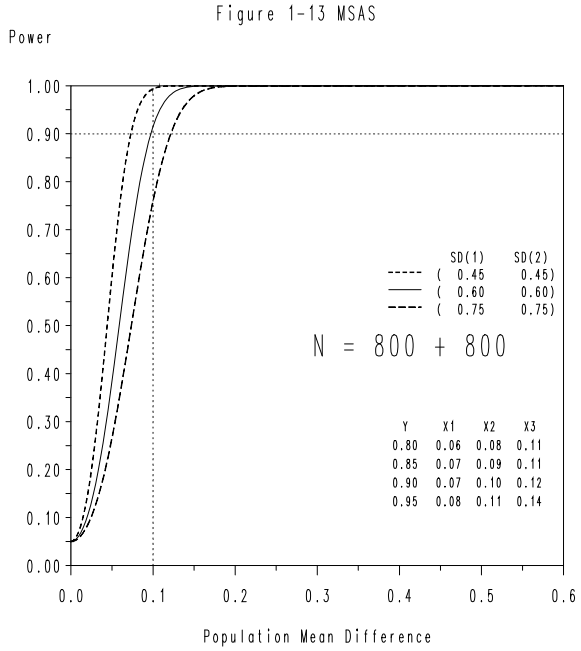


Figure 1-14 MSAS

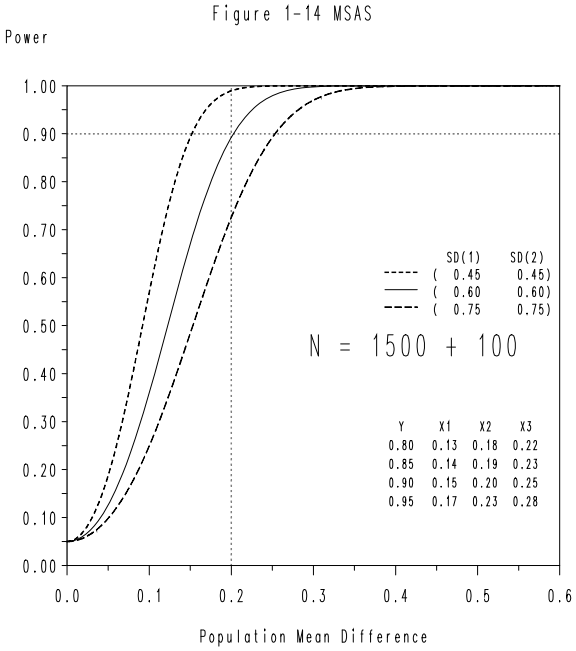


Figure 1-15 MSAS

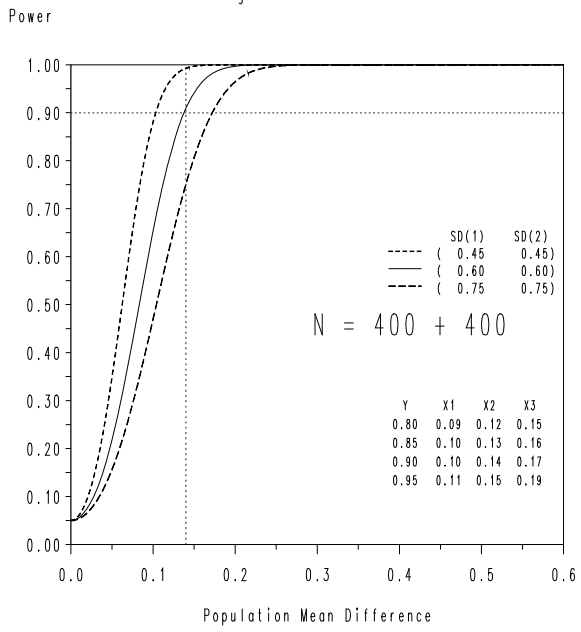


Figure 1-16 MSAS

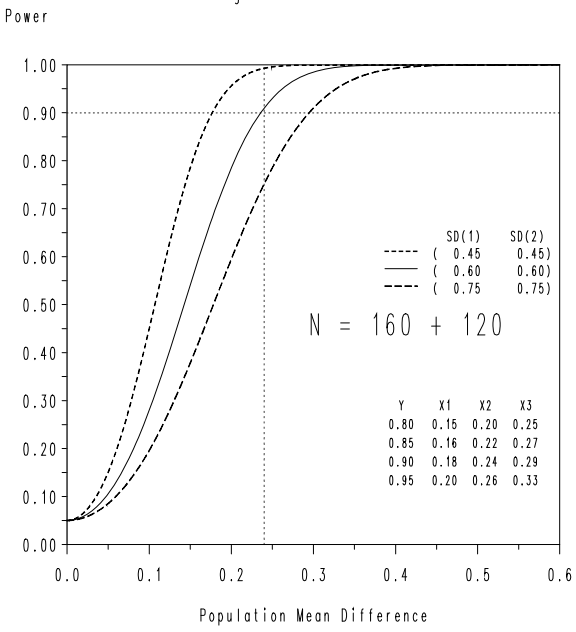


Figure 1-17 MSAS

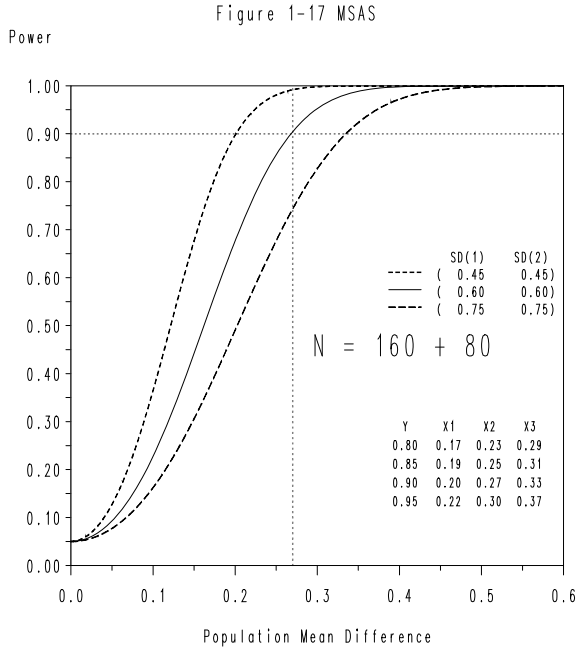


Figure 1-18 MSAS

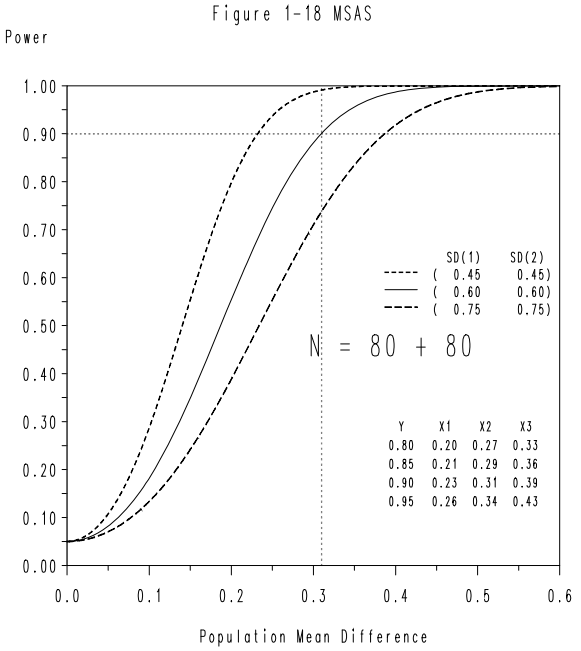


Figure 1-19 MSAS

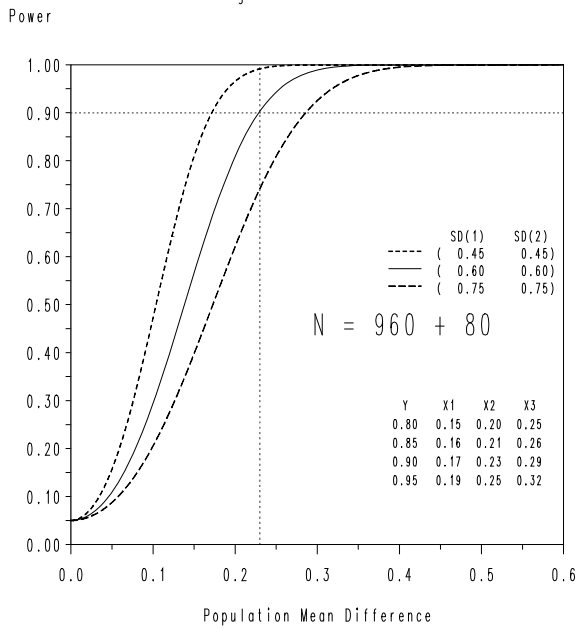


Figure 1-20 MSAS

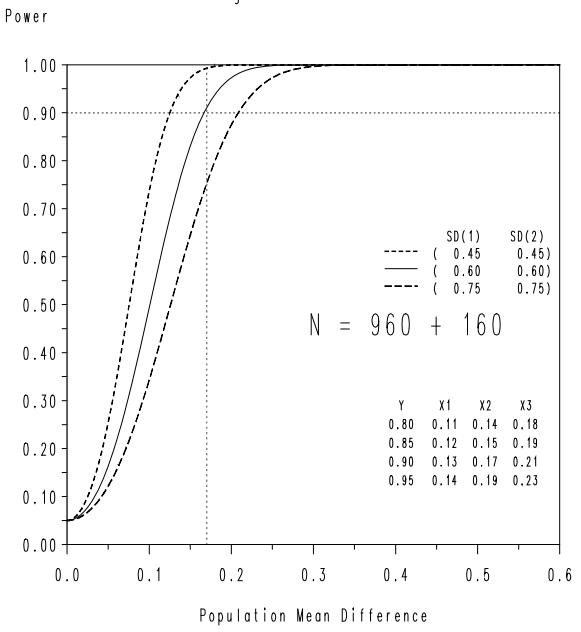


Figure 2-1 PROMIS

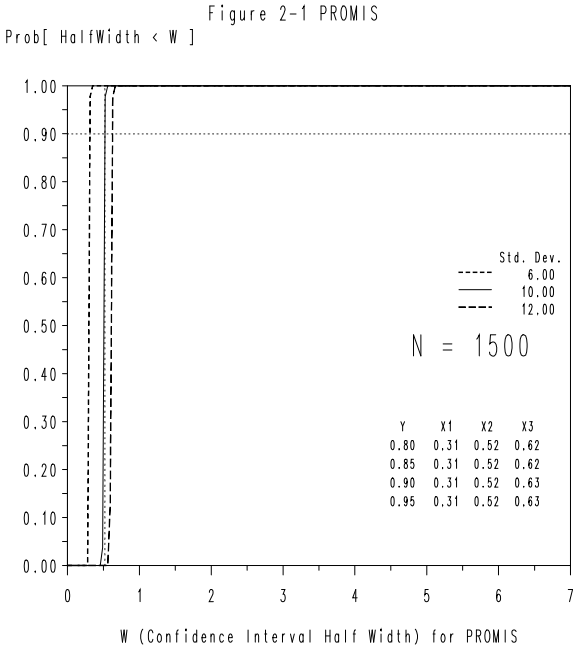


Figure 2-2 PROMIS

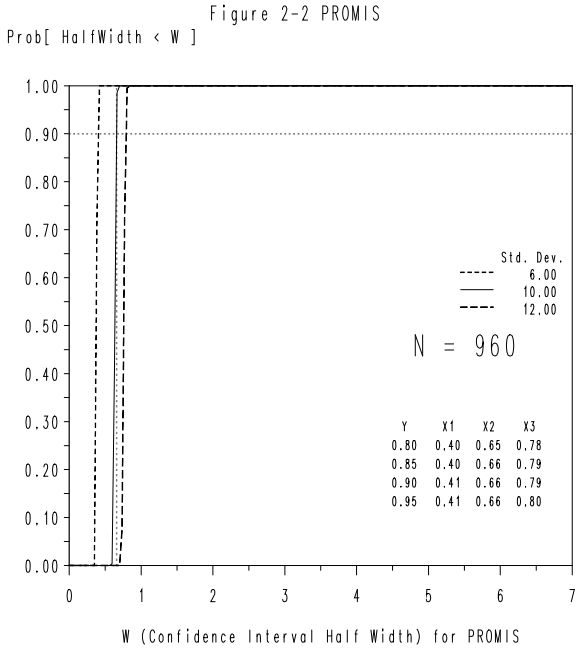
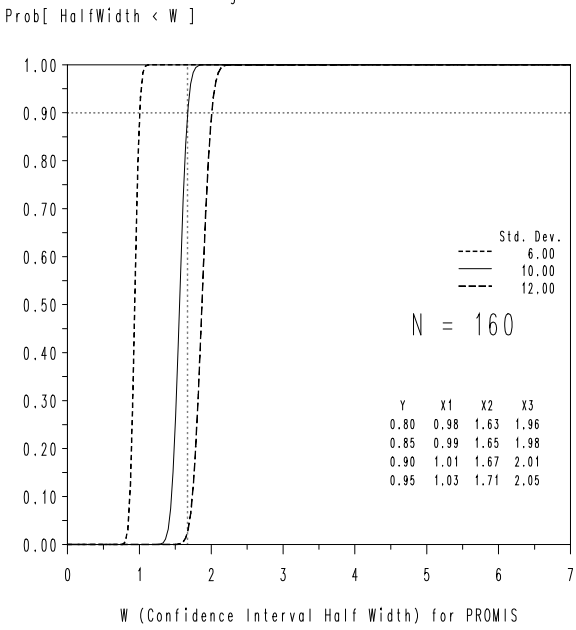


Figure 2-3 PROMIS



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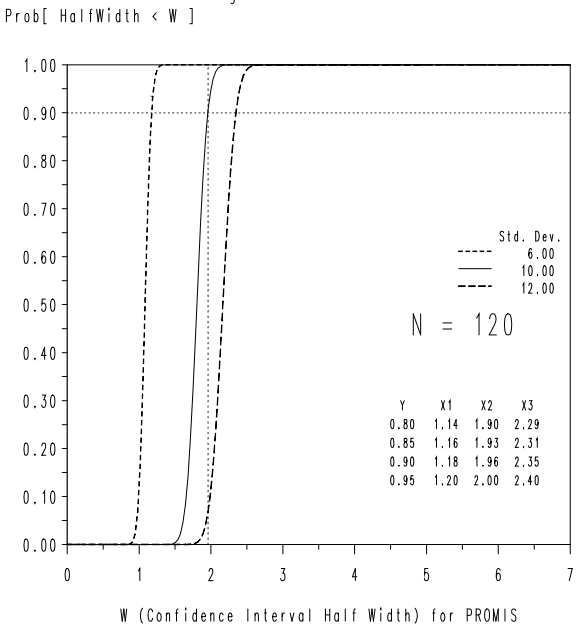

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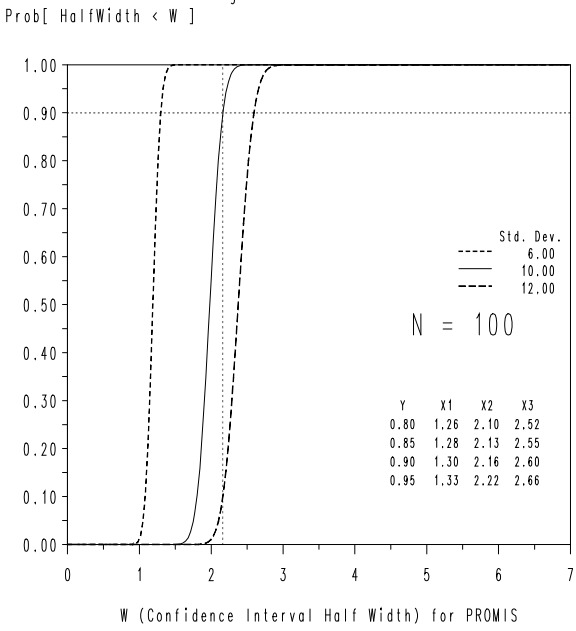

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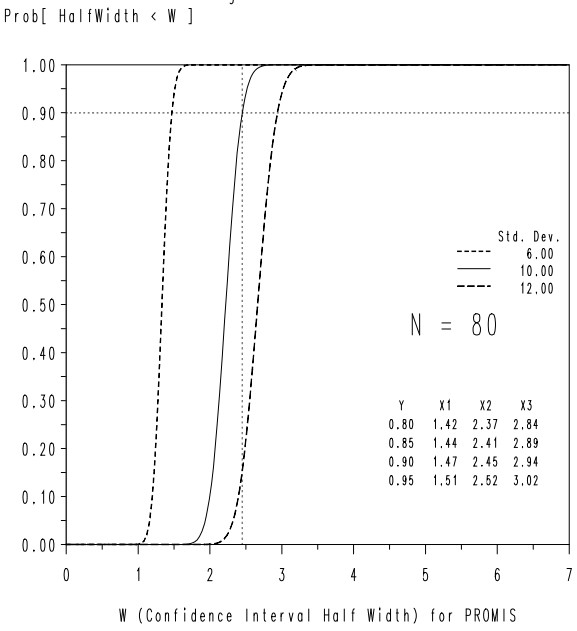

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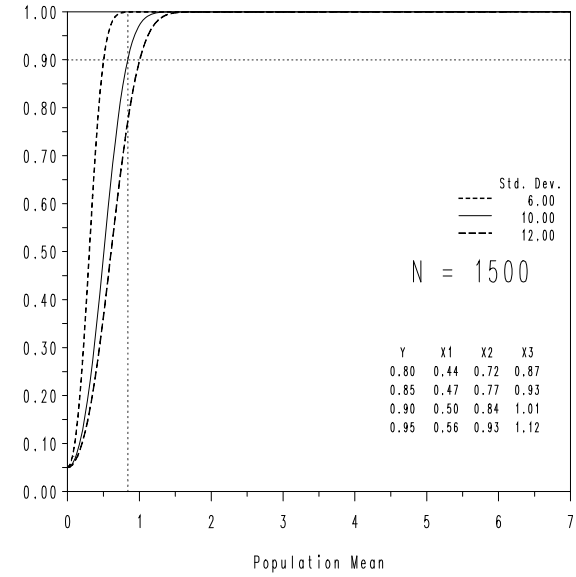

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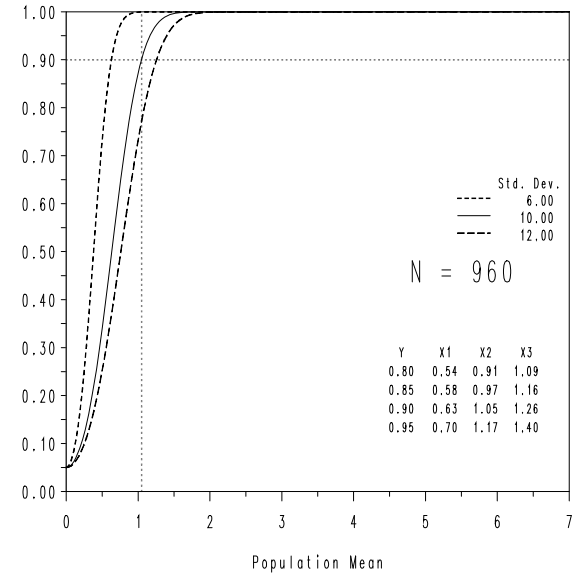

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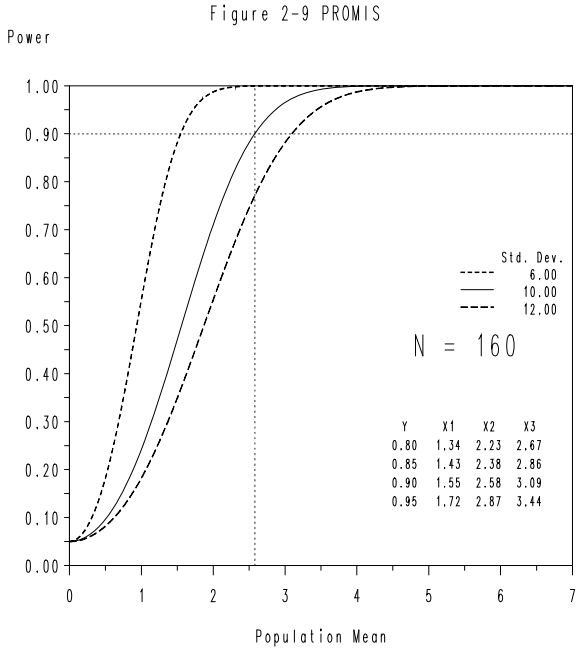
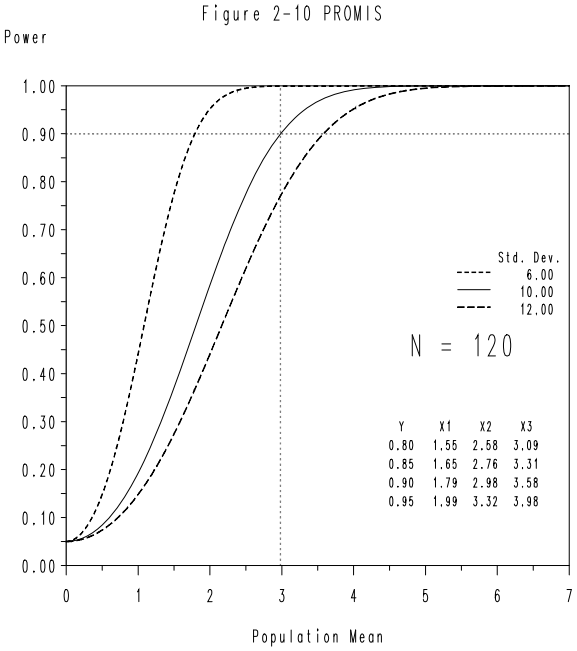


Figure 2-10 PROMIS



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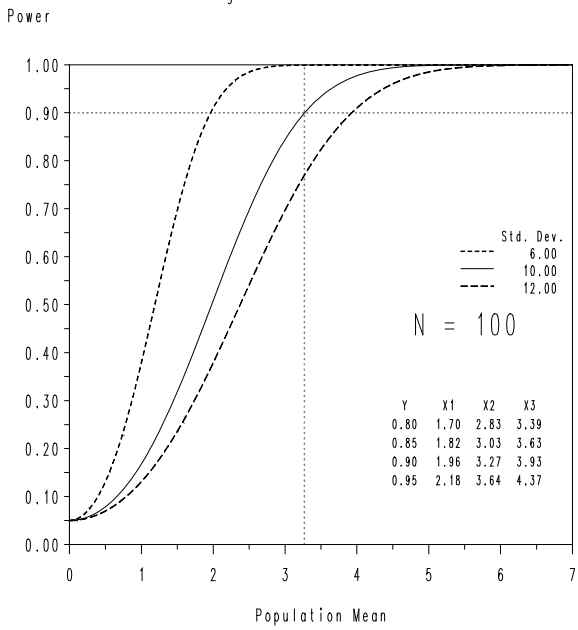

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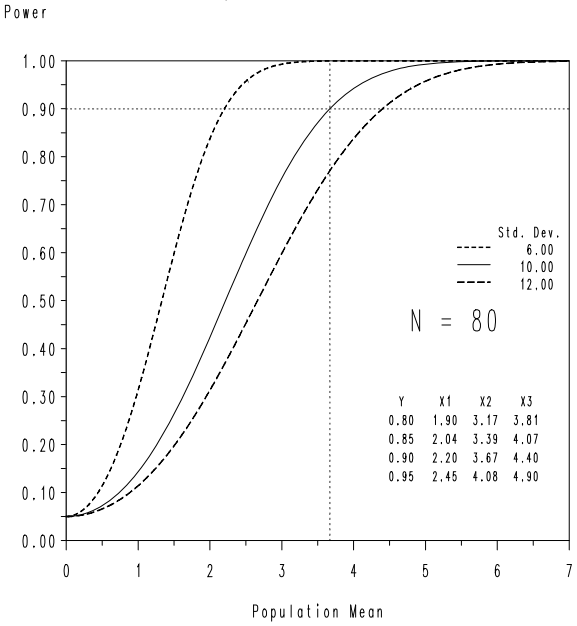

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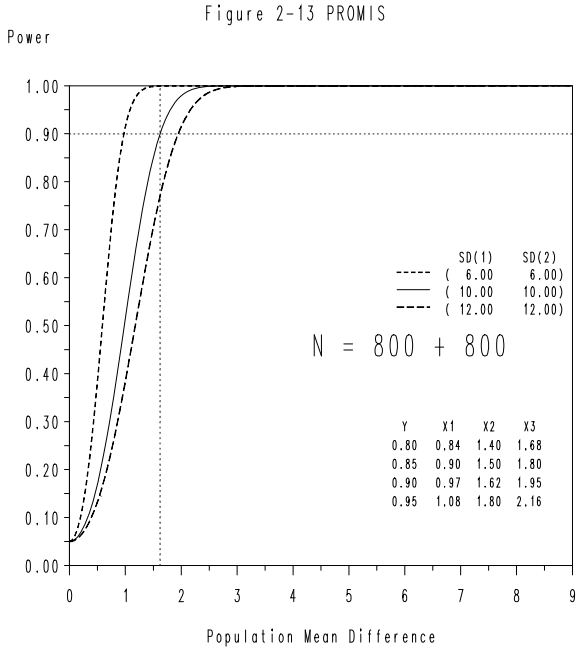

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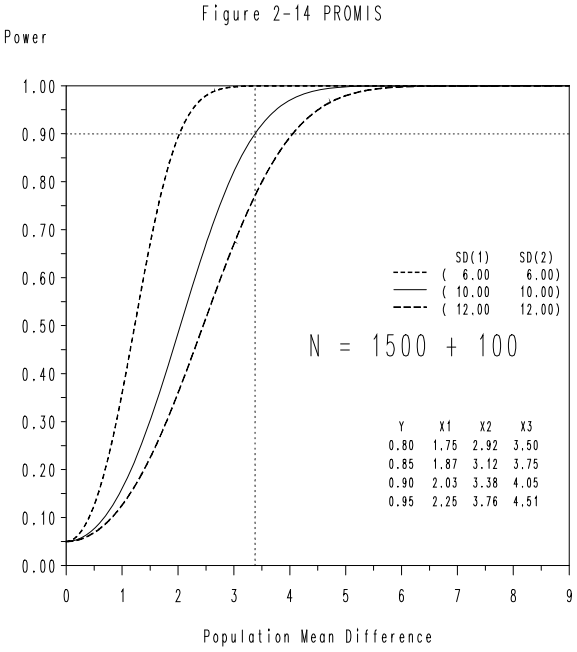

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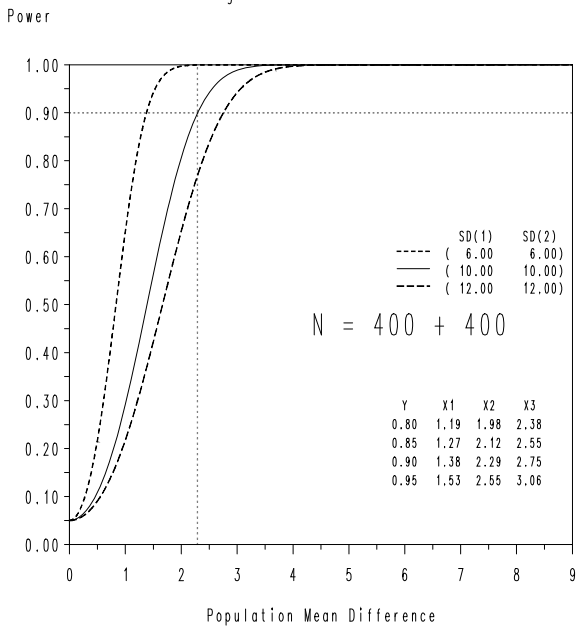
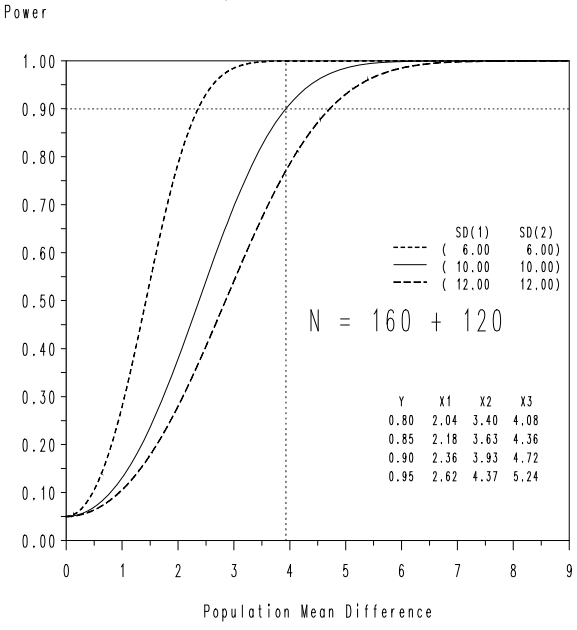


Figure 2-16 PROMIS



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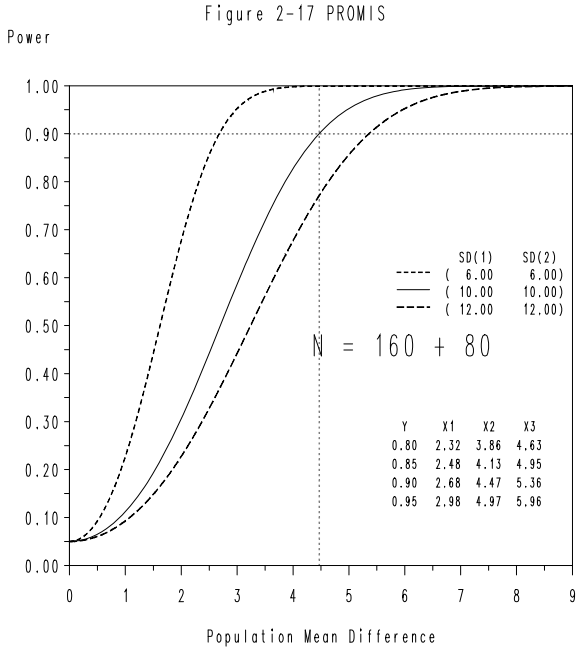
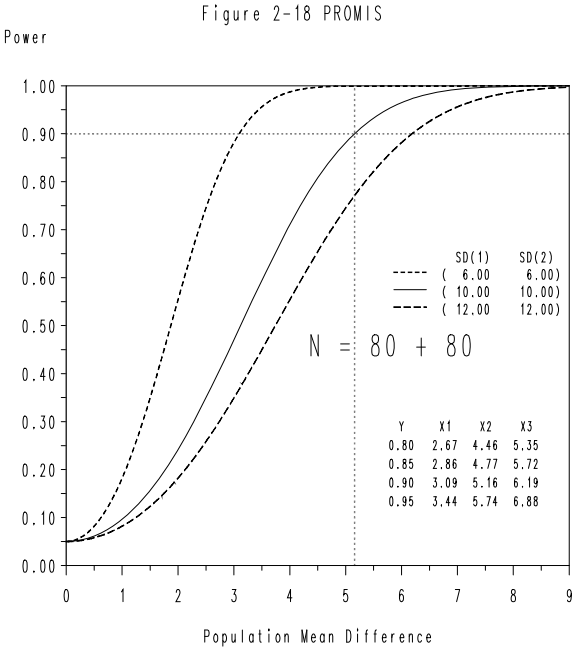


Figure 2-18 PROMIS



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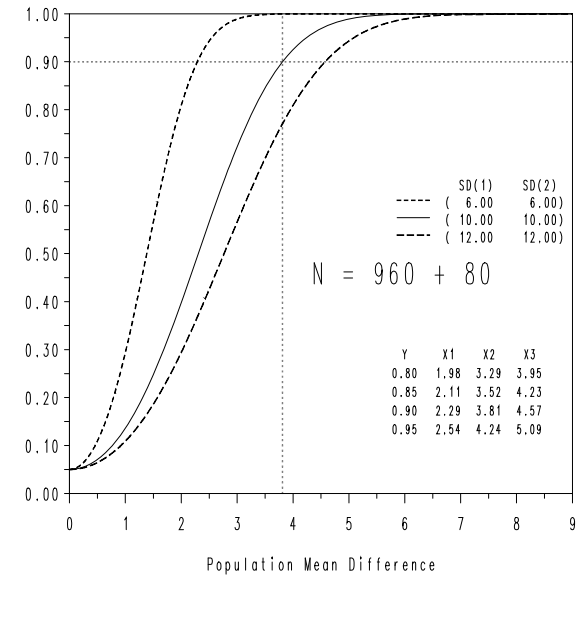


Figure 2-20 PROMIS

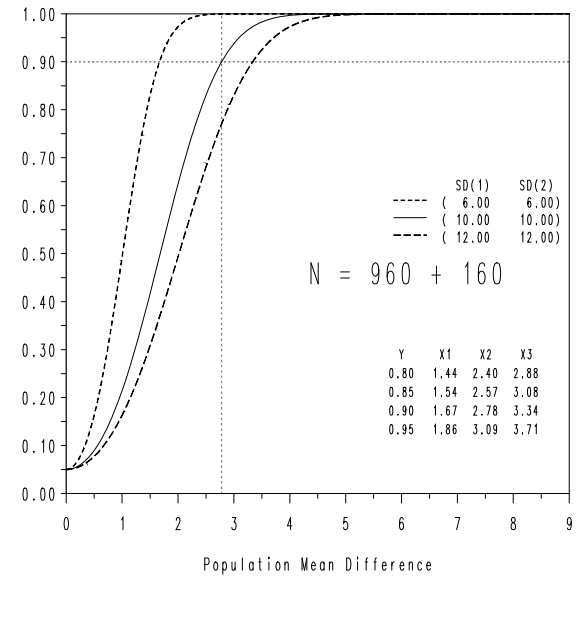


Figure 3-1 HCV-PRO

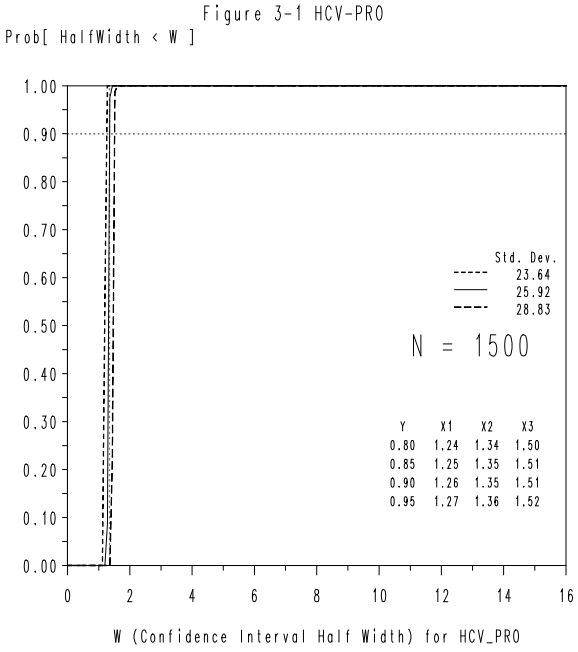


Figure 3-2 HCV-PRO

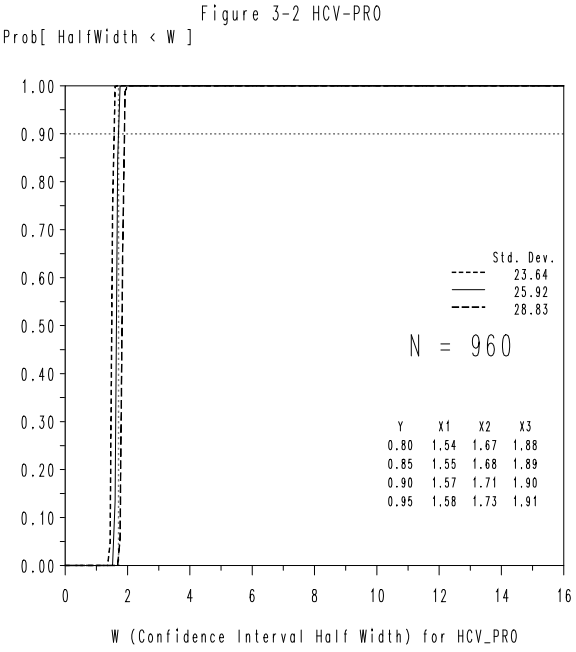


Figure 3-3 HCV-PRO

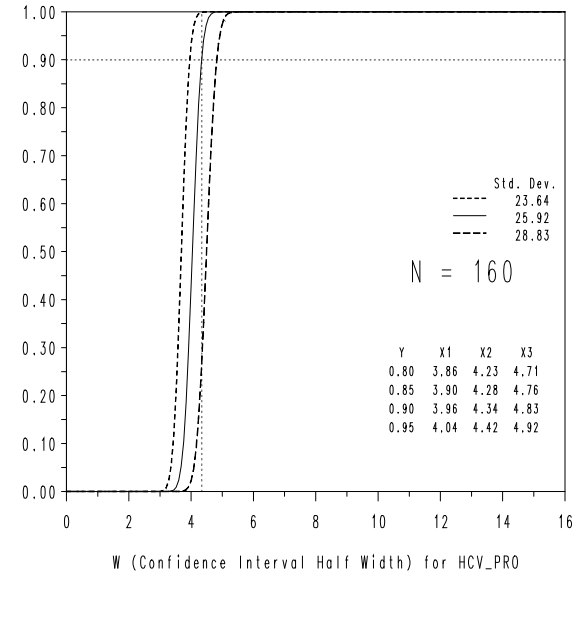


Figure 3-4 HCV-PRO

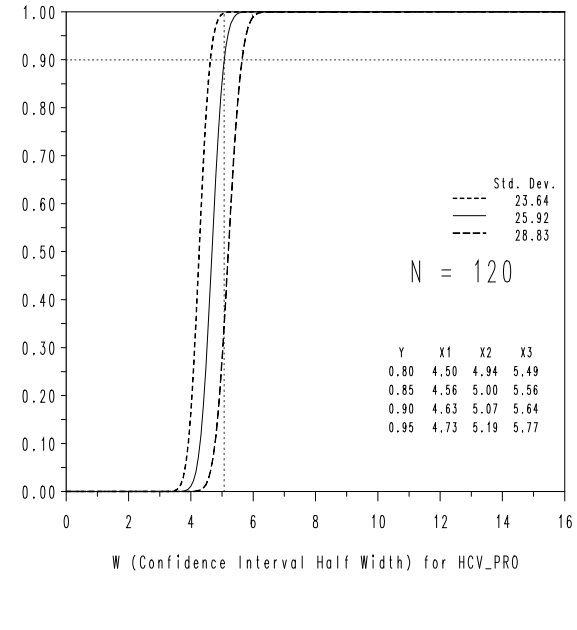
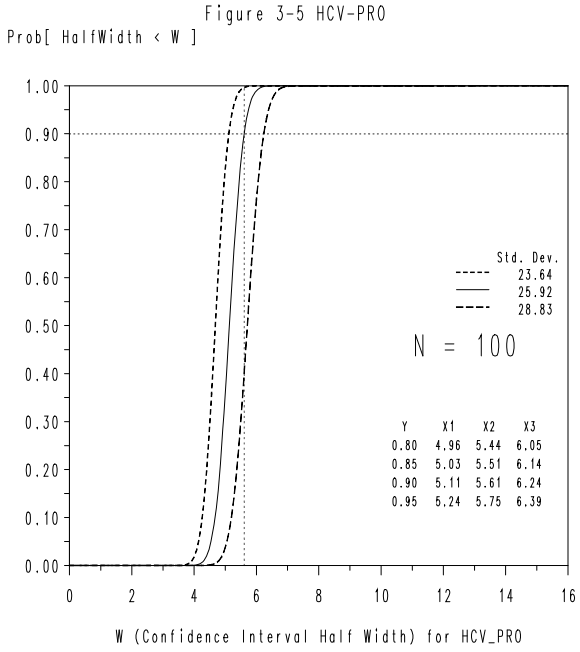


Figure 3-5 HCV-PRO



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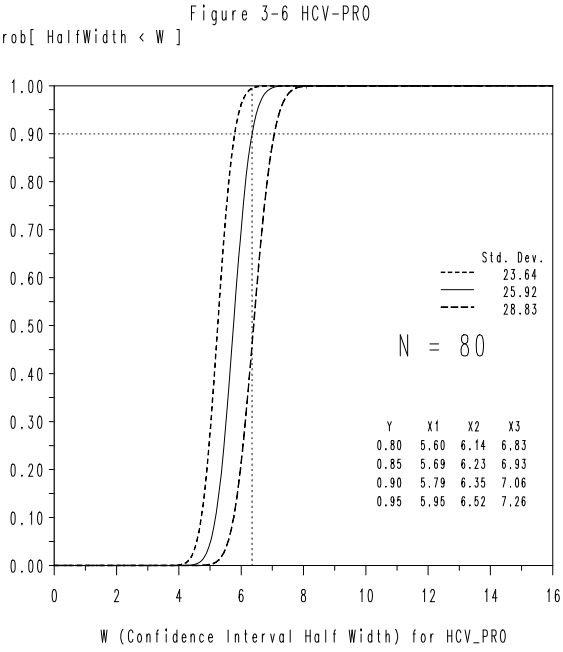

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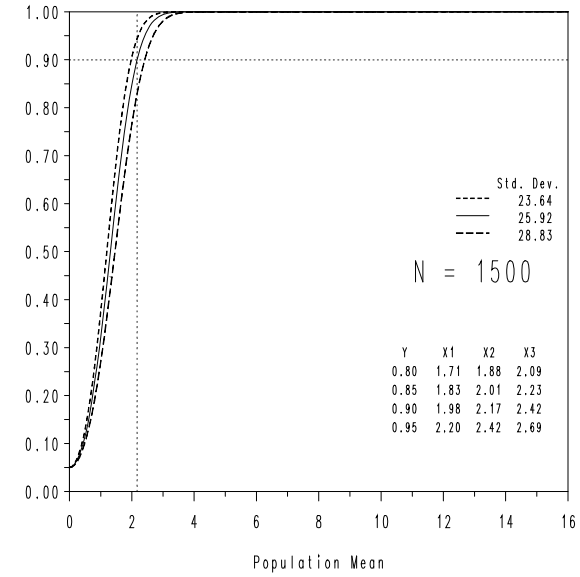

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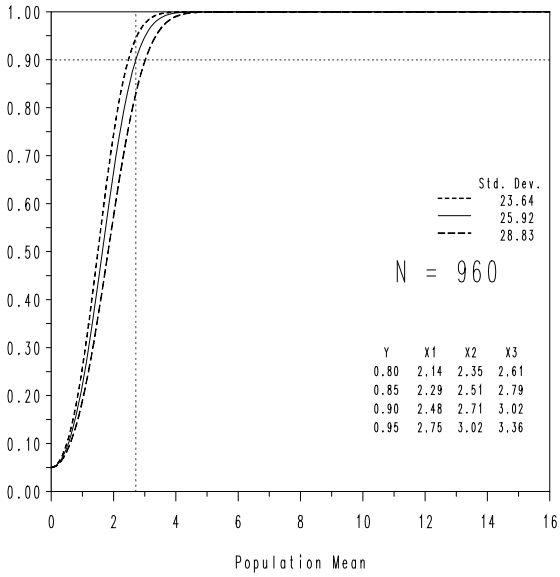

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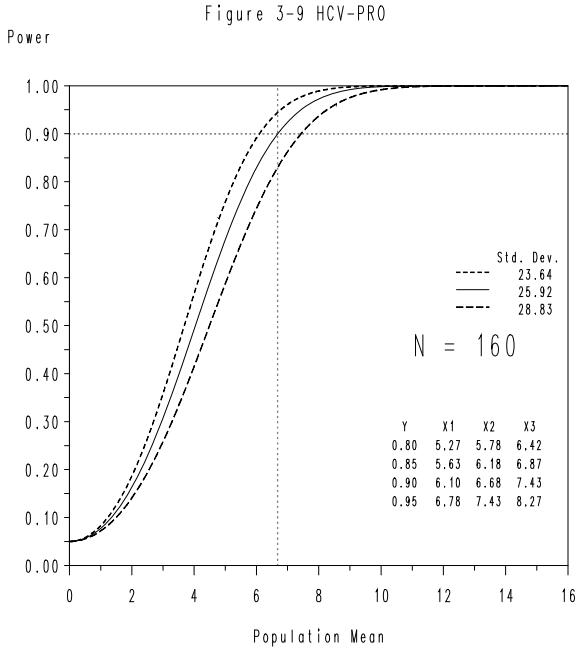

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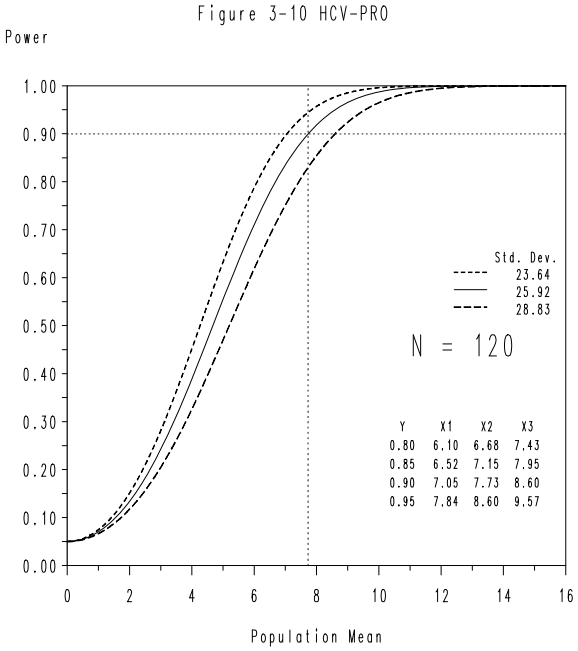
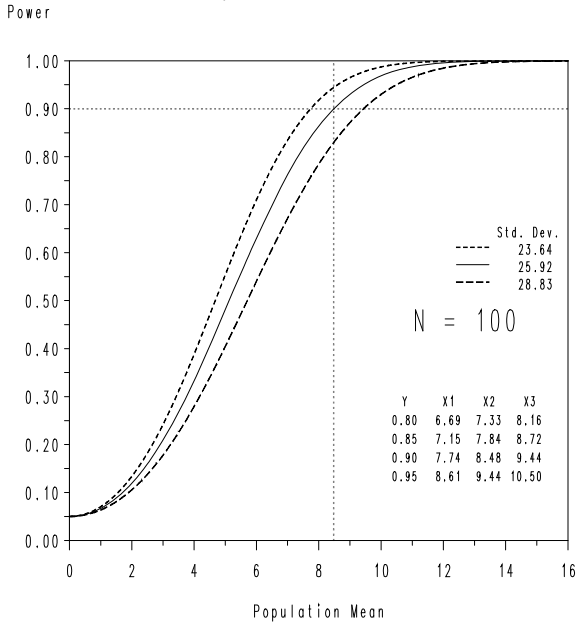


Figure 3-11 HCV-PRO



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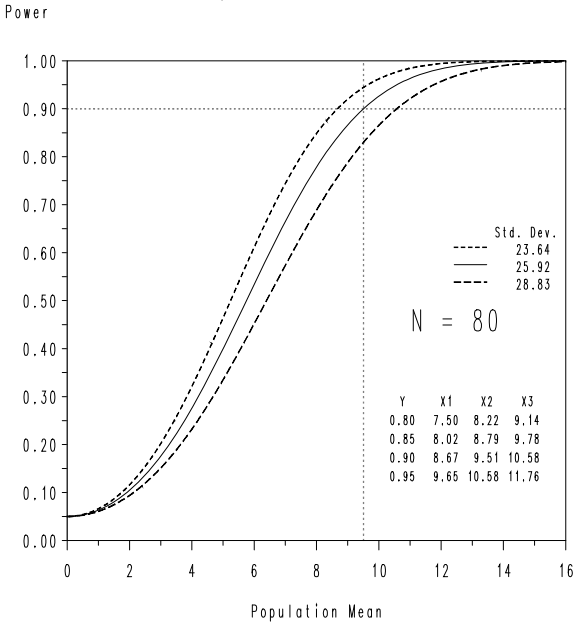

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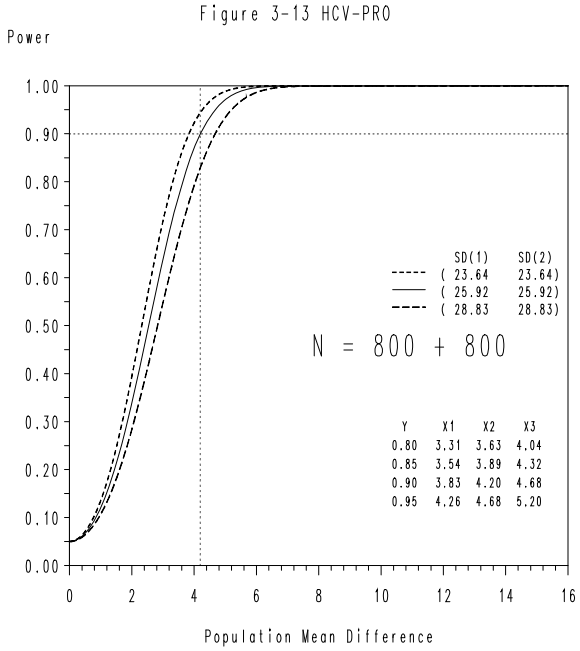


Figure 3-14 HCV-PRO

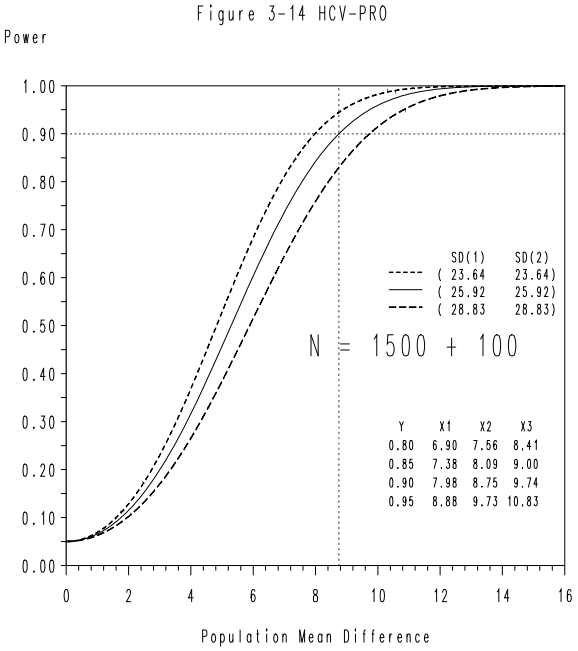


Figure 3-15 HCV-PRO

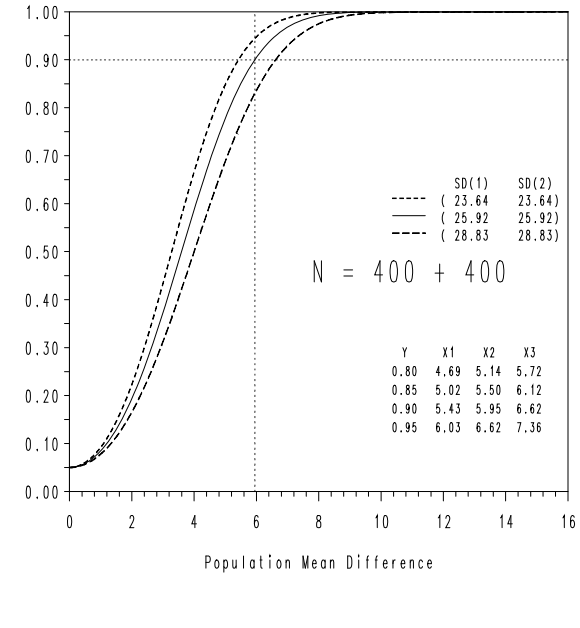


Figure 3-16 HCV-PRO

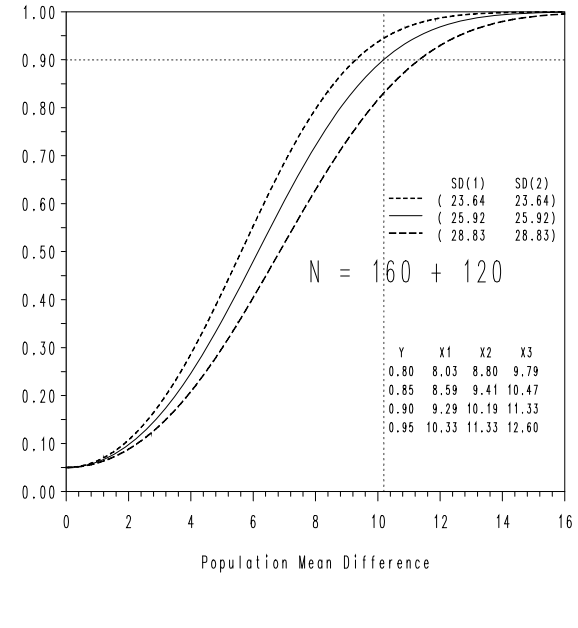


Figure 3-17 HCV-PRO

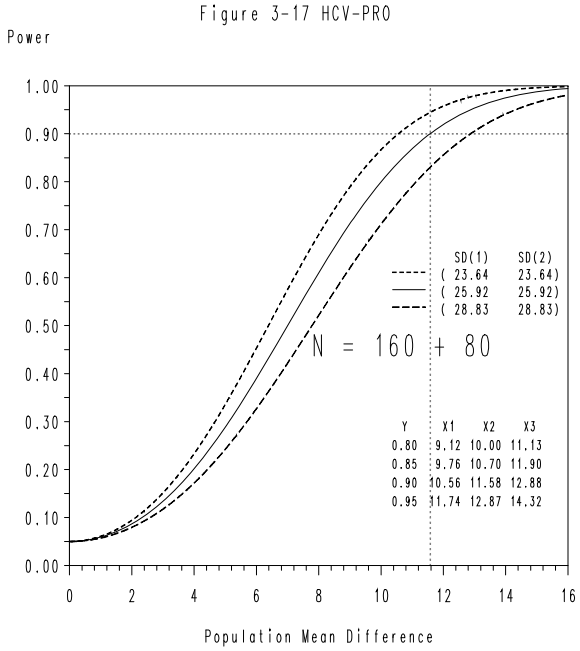
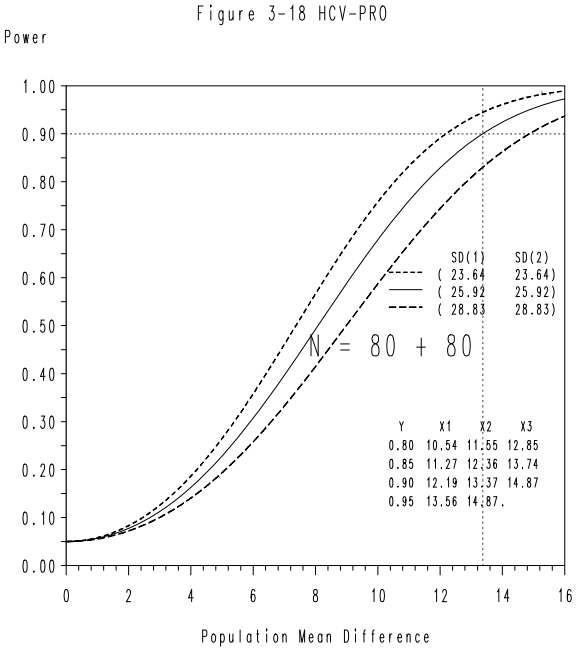


Figure 3-18 HCV-PRO



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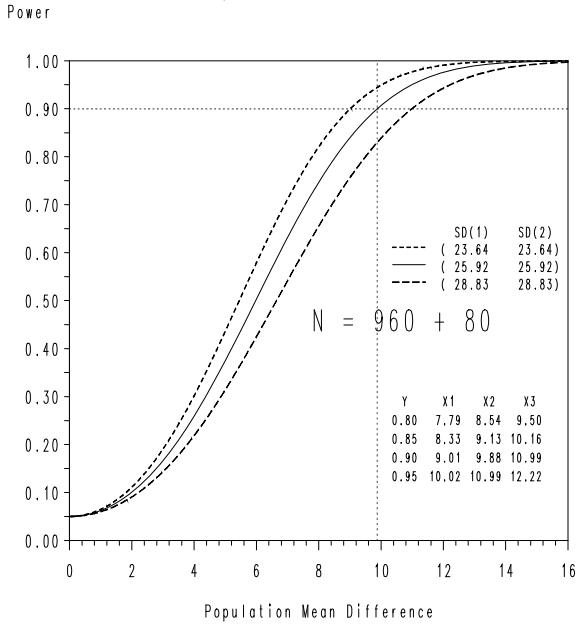


Figure 3-20 HCV-PRO

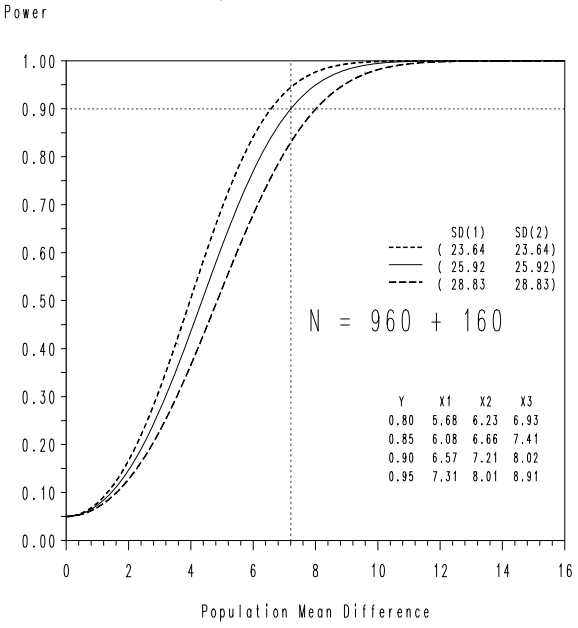


Figure 4-1 ADHERENT

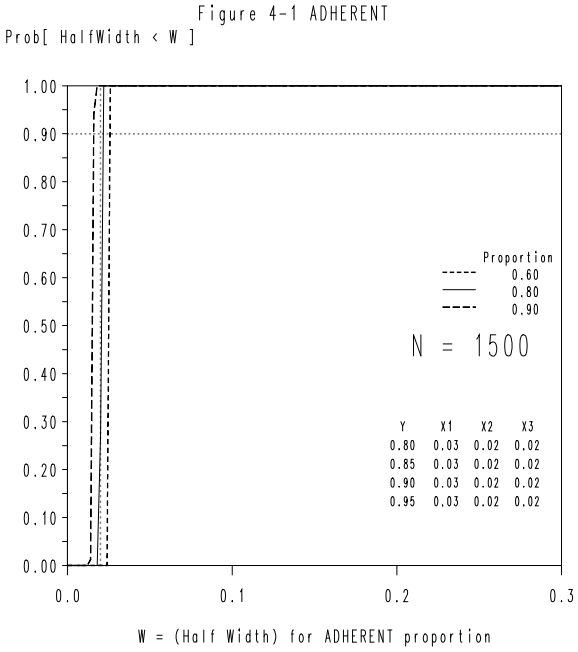


Figure 4-2 ADHERENT

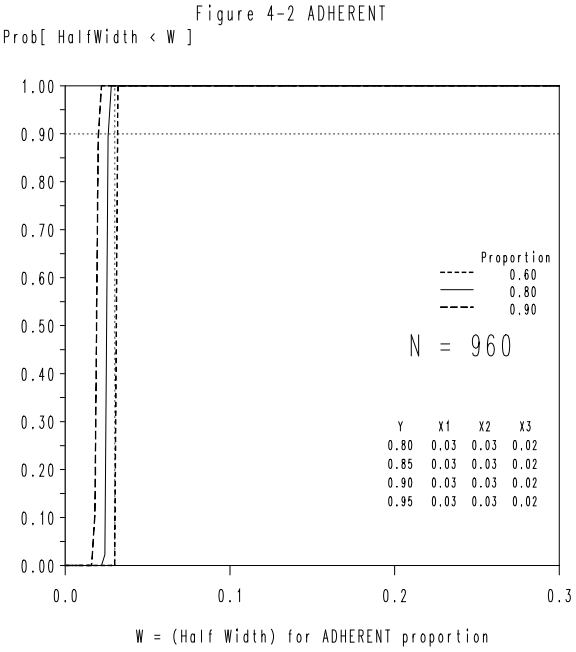


Figure 4-3 ADHERENT

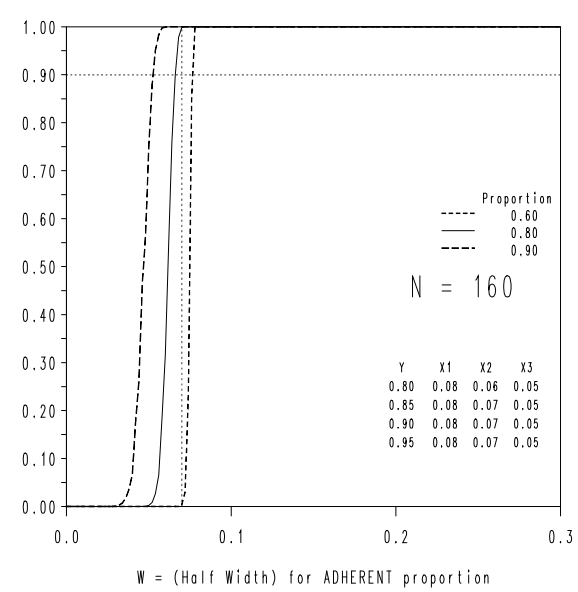


Figure 4-4 ADHERENT

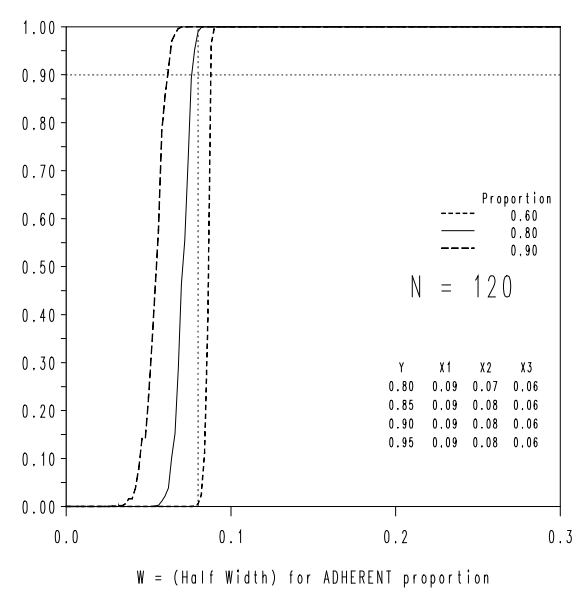
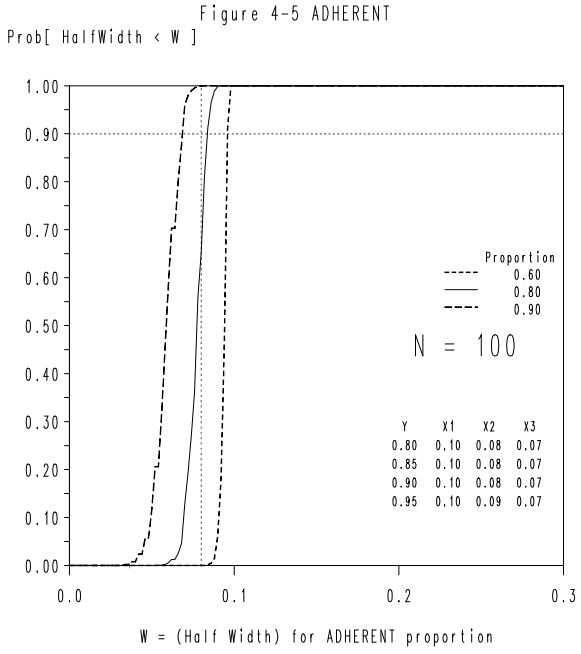


Figure 4-5 ADHERENT



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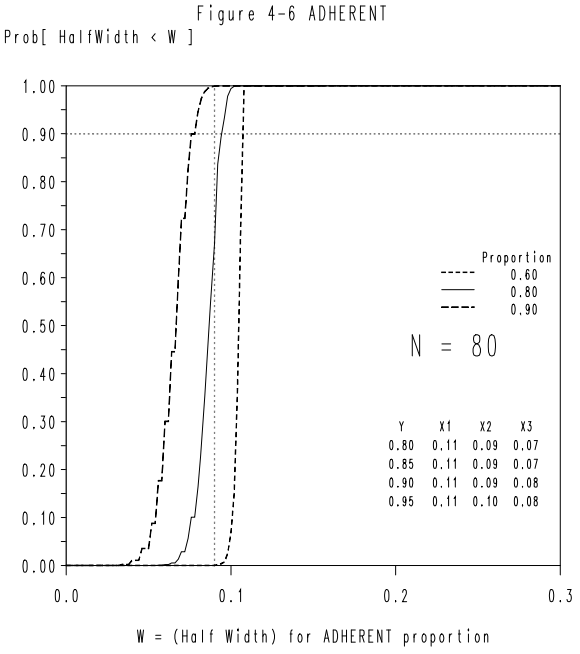

Figure 4-7 ADHERENT

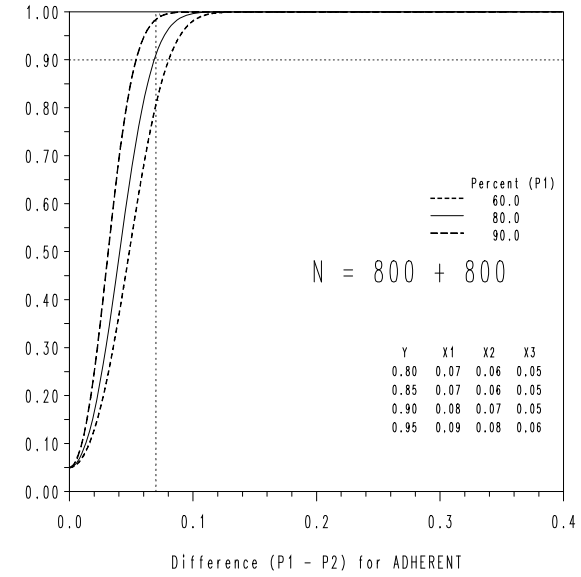

Figure 4-8 ADHERENT Eq