Role of Pegylated Interferon in Combination With DAAs to Cure Hepatitis C As Soon As Possible - Hepatitis C (ASAP-C)

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Principal Investigators
Shruti H. Mehta, PhD MPH
Sunil S. Solomon MBBS, PhD MPH

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1. Abstract

Globally, there are approximately 70 – 80 million persons with chronic hepatitis C (HCV) virus infection. Chronic hepatitis C is treatable and treatment can cure infection. Treatment access has been hampered in much of the world due to the low efficacy and toxicity of the previous generation of regimens. The landscape of HCV treatment has changed dramatically with the recent US FDA approval of highly efficacious, non-toxic second generation direct acting antiviral agents. With these advances in treatment, conversations about elimination and global eradication of HCV have begun. As part of these discussions, questions have arisen about delivery of these agents among populations in resource-limited settings (RLS) and among populations that have historically had adherence challenges. Ideally, a treatment regimen for RLS should be pan-genotypic; thereby, not requiring HCV genotype testing which can be cost prohibitive and rarely available in these settings. In addition, in populations where adherence can be challenging such as people who inject drugs (PWID), duration should be as short as possible and the ideal regimen should be forgiving of missed doses.

We recently completed a pilot study comparing the first two pangenotypic HCV treatment regimens approved for use in India among a population with a history of injection drug use. These two regimens were: sofosbuvir + ribavirin + pegylated interferon 2a (SOF+PR) for 12 weeks and sofosbuvir + ribavirin for 24 weeks (SOF+R). Both regimens were delivered using a field-based directly observed therapy (DOT) approach. While interferon injections were delivered once weekly in a clinic, all doses of sofosbuvir and ribavirin were dosed in the field by a field worker at a location chosen daily by the participant. Among 50 persons randomized, 88% completed treatment in both arms. However, sustained virologic response at 12 weeks (SVR12) was significantly higher in the SOF+PR arm compared to the SOF+R arm (88% vs 60%). Moreover, no participants in the SOF+PR arm who completed treatment failed therapy. This was despite ongoing substance use in 52% and a median of 2 (Range: 0-18) missed doses in those who completed therapy in the SOF+PR arm. By contrast, in the SOF+R arm, SVR12 was significantly lower among persons who were actively using drugs or alcohol and who missed >5% of doses. While our trial suggested that field-based DOT was feasible in general, there were logistical challenges that we encountered raising questions about whether this is the optimal strategy for all patients. Moreover, since this trial was completed, new generic direct acting antivirals (DAAs) have become available globally and in India and new data have emerged on the efficacy of shorter duration regimens that include 2 DAAs and pegylated interferon. *Accordingly, we will conduct a second pilot trial to compare a shortened 4-week regimen that includes pegylated interferon and two DAAs to an all-oral 12-week pan-genotypic regimen both delivered using DOT and a third arm which will comprise SOF/daclatasvir (DAC) delivered as per standard of care.*

2. Objectives

The primary objective of this study is:

1) To compare the efficacy, measured as sustained virologic response (SVR) at least 12 weeks after completion of therapy, across three study regimens/delivery modalities: ARM 1 – 4 weeks of sofosbuvir (SOF) + daclatasvir (DAC) + pegylated interferon alfa-2a (PEG) delivered using DOT; ARM 2 – 12 weeks of SOF+DAC delivered using DOT; and ARM 3 – 12 weeks of SOF+DAC delivered as per standard of care (monthly dispensation with no DOT).

Secondary objectives are:

1) To compare adherence among persons across the three study arms.
2) To evaluate the safety, tolerability and acceptability of treatment in the three arms.

3. Background

Globally, an estimated 70 – 80 million persons are chronically infected with hepatitis C (HCV). Chronic hepatitis C is associated with long-term complications including liver cirrhosis, hepatocellular carcinoma and end-stage liver disease. Chronic hepatitis C is treatable and treatment can cure infection such that HCV RNA is undetectable and persons cannot transmit virus and risk for chronic complications decreases substantially. Treatment access has been hampered in much of the world in part due to the low efficacy and toxicity of the previous generation of regimens. The landscape of HCV treatment has changed dramatically over the past few years with the FDA approval of highly efficacious, non-toxic second generation direct acting antiviral agents. With these advances in treatment, questions have arisen about delivery of these agents among populations in resource-limited settings (RLS) given some of the inherent differences in HCV infected patients in these settings. Ideally, a treatment regimen for RLS should be pan-genotypic; thereby, not requiring HCV genotype testing which can be cost prohibitive and rarely available in these settings. Moreover, treatment delivery strategies need to optimize adherence particularly in populations that have had suboptimal adherence such as people who inject drugs (PWID).

We recently completed a pilot trial comparing directly the two first available pan-genotypic regimens in India (SOF+PR for 12 weeks and SOF+R for 24 weeks). We used a field-based directly observed therapy (DOT) delivery strategy. While interferon injections for the SOF+PR arm were delivered once weekly in a clinic, all doses of sofosbuvir and ribavirin were dosed in the field by a field worker at a location chosen daily by the participant. Among 50 persons randomized, 88% completed treatment in both arms. However, sustained virologic response at 12 weeks (SVR12) was significantly higher in the SOF+PR arm compared to the SOF+R arm (88% vs 60%). Moreover, no participants in the SOF+PR arm who completed treatment failed therapy. This was despite ongoing substance use in 52% and a median of 2 (Range: 0 -18) missed doses in those who completed therapy in the SOF+PR arm. By contrast, in the SOF+R arm, SVR12 was significantly lower among persons who were actively using drugs or alcohol and who missed >5% of doses. Notably, no serious adverse events occurred in the SOF+PR arm and no one discontinued therapy in the SOF+PR arm due to side effects. While our trial suggested that field-based DOT was feasible in general, there were logistical challenges that we encountered raising questions about whether this is the optimal strategy for all clients. Further, as all patients received DOT the role of DOT itself could not evaluated. Moreover, since this trial was completed, new generic direct acting antivirals (DAAs) have become available in India and new data have emerged on the efficacy of shorter duration regimens that include 2 DAAs and pegylated interferon. In the 4WIDUC study conducted among PWID in Amsterdam, a 4-week regimen of SOF+ ledipasvir+ pegylated interferon+ ribavirin was associated with an SVR of 94%. Of note, 15/16 patients randomized to this arm completed treatment and all achieved SVR – one patient was lost to follow-up. All patients were on opioid agonist therapy and the comparator arm was another experimental arm and not per guidelines.

Accordingly, we propose to conduct a pilot trial among people who inject drugs in India that evaluates the efficacy of a shortened 4-week regimen including pegylated interferon and two DAAs to an all-oral 12-week pan-genotypic regimen with both delivered using DOT and a third arm which will comprise SOF/DAC delivered as per standard of care. Further, we will also estimate cost per SVR in each of these three arms as costs associated with DOT could potentially offset the benefit. These data will provide critical insight into the optimal delivery strategy for people who use drugs in resource limited settings.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures
This will be a non-blinded randomized clinical trial with 150 participants randomized at a 1:1:1 allocation ratio to one of three treatment arms.

Arm 1: Sofosbuvir (400mg/daily) + Daclatasvir (60mg/daily) + Pegylated Interferon alfa-2a (180µg/weekly) for 4 weeks with a field-based DOT approach

Arm 2: Sofosbuvir (400mg/daily) + Daclatasvir (60mg/daily) for 12 weeks with a field-based DOT approach

Arm 3: Sofosbuvir (400mg/daily) + Daclatasvir (60mg/daily) for 12 weeks with standard of care dispensation (4 monthly doses)

Pegylated-interferon alfa-2a (PEG) will be delivered subcutaneously once weekly. Sofosbuvir (SOF) and Daclatasvir (DAC) will be taken orally once daily for the entire study period.

The study will take place at the YR Gaitonde Centre for AIDS Education and Johns Hopkins University Collaborative Integrated Care Center (YRG-JHU ICC) located within the premises of the Chattisgarh Institute of Medical Sciences (CIMS) in Bilaspur in the state of Chattisgarh, India. Our team of investigators from Johns Hopkins and YRG CARE has collaborated since 1998 and our team has collaborated with CIMS since 2014. The YRG-JHU ICC in CIMS is a site in an ongoing cluster-randomized trial (IRB # IRB00082575) and as part of this trial, we have recruited >1,000 PWID using respondent-driven sampling (RDS) for an epidemiological assessment. The YRG-JHU ICC is essentially a part of a service delivery intervention; all clients are provided with services free-of-charge as needed: 1) HIV counseling and testing; 2) linkage to antiretroviral therapy; 3) opioid substitution therapy; 4) syringe exchange; 5) TB screening and referral; 6) STI testing and management; 7) counseling services; and 8) hepatitis C testing. We have also delivered services to 1115 PWID through an integrated care centre (ICC). This trial will be conducted within the YRG-JHU ICC.

4a1. Recruitment

Participants will be recruited from the YRG-JHU ICC in Bilaspur, which currently has 514 registered HCV antibody positive clients. The Bilaspur ICC is in the Chattisgarh Institute for Medical Sciences (CIMS) and delivers 8 key services described above.

We will recruit from the subset of participants who test positive for HCV antibodies at the YRG-JHU ICC or who present confirmation of HCV infection from another source. The YRG-JHU ICC Nurse will work with the YRG-JHU ICC Site Coordinator and YRG-JHU ICC Counselor to identify potentially eligible ICC clients and provide brief information about the study to potentially eligible study subjects. They will introduce the study in a private room at the Bilaspur ICC to preserve privacy and confidentiality. In addition, flyers will be posted in the Bilaspur ICC so that participants may self-refer. They will refer potentially eligible participants to the ASAP-C Study Nurse. All of these staff members have been working with PWID for many years and are sensitive to the challenges within this population. We have opted to use the existing ICC staff to help with recruitment efforts because the population is very comfortable with this staff.

4a2. Visit Schedule

All subjects will complete screening, baseline, end-of treatment and post-treatment assessments. All of these assessments will take place in the YRG-JHU ICC in Bilaspur. Screening assessments will be completed within 28 days of the Baseline/Day 1 visit. Participants in all three arms will be asked to complete 4 study visits: 1) Screening; 2) the Baseline/Day 1 of treatment visit; 3) End of treatment visit (at 4 weeks for participants in Arm 1 and at 12 weeks for participants in Arms 2 and 3); and 4) 12 weeks post treatment completion visit (SVR12). In addition, subjects in Arm 1 will need to visit the clinic for an additional 3 visits to receive their PEG injections and participants in Arm 3 will need to come in at Weeks 4 and 8 for medication refills. Finally, subjects in Arms 1 and 2 will receive daily visits from field staff to receive their study medications.

The details of procedures at each visit are listed below. Information on laboratory parameters to be measured and details regarding the clinical assessments that will be performed are provided in *4a5.6*.

4a3. Screening and Consent Procedures

Subjects will complete all screening assessments within 28 days of the Baseline/Day 1 visit. Written informed consent will be obtained from subjects prior to the assessment of study eligibility. Those who fail to satisfy eligibility criteria for the trial will still be able to receive services provided by the ICC. If they are still visiting the ICC, they will be allowed to re-screen for the pilot trial if they were excluded because of a modifiable exclusion criteria (e.g., Platelet count <50,000 cells/ml).

The study will be described to all potentially eligible subjects in a private room by the YRG-JHU ICC site coordinator or the YRG-JHU ICC Nurse and all interested participants will be referred to the ASAP-C study nurse for informed consent. Written informed consent will be obtained from all potentially eligible subjects prior to conducting any screening assessments. A single written informed consent will be utilized for the screening protocol and study procedures. The consent will be translated into Hindi (local language) and delivered in Hindi. Potential study subjects will be offered a copy of the consent form, but we anticipate that a high proportion of potential subjects will be illiterate. The consent will be delivered in a private room by a study nurse. The consent will address in-depth the screening procedures, randomization, the three different treatment arms and potential adverse events of study treatments, and the follow-up protocol for the study. We will allow approximately 1 to 1.5 hours for delivering the consent and responding to questions.

Our study staff has been working with this population for the past 3 years and so has substantial experience in ascertaining whether the potential study participant has understood all of the relevant information in the consent. The potential study participant will be given multiple opportunities to ask questions and will be able to speak with both the study doctor and the study counselor, if the nurse is unable to clarify his/her questions satisfactorily.

Fingerprint (biometric) data will be collected from all subjects who agree to take part in the study, if not already available at the ICC. Biometric data is the standard of care to track participants at the ICCs. The image of each of the subject's fingerprints will be scanned and converted into a unique code of numbers and letters – the image itself will not be stored. The generated code will serve as the subject's unique ID and it will be used to link the subject to their study ID. For all follow-up visits (and daily DOT dosing), subjects will scan their fingerprint to confirm identity before all necessary study procedures are carried out. Fingerprint generated codes for follow-up are currently being used to track participants in the ICC.

In addition to consent and fingerprint collection, additional procedures that will be conducted at the Screening visit include:

- Obtaining medical history
- Obtaining details of concomitant medications and adverse events
- Performing complete physical examination (including retinal examination)
- Obtaining vital signs
- Obtaining body weight and height
- Obtaining blood samples for the tests listed in Table 3
- Obtaining urine sample for β-hCG pregnancy test for females of childbearing potential only
- Chart review of YRG-JHU ICC data to document HIV and antiretroviral therapy status and engagement in opioid substitution therapy (OST)

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will return to the clinic for the Baseline/Day 1 visit assessments and randomization.

4a4. Randomization

A random treatment allocation list will be prepared by a staff member who is not involved in the study using a commercial statistical software package. Blocked randomization will be performed using blocks of randomly

varying sizes of 3, 6 and 9 at a 1:1:1 allocation ratio between the three arms. Blocked randomization will ensure equal distribution of participants between the three arms even if the targeted recruitment numbers are not met. Further, using a variation in the block sizes will minimize the possibility of the study staff being able to identify which arm the next subject would be allocated to. Treatment assignments will be transferred to numbered, opaque, sealed study envelopes by a staff member who is not involved with the study. Envelopes will be opened sequentially by the study physician or research manager as subjects are enrolled. Biometric information (fingerprint data) of the study participant will be recorded prior to randomization assignment.

4a5. Treatment Assessments

4a5.1. Baseline / Day 1 Visit

The following procedures will be completed prior to randomization and dosing/dispensing.

- Perform targeted physical examination
- Obtain vital signs
- Obtain body weight
- Assessment of adverse events and concomitant medications
- Pregnancy prevention counseling for female participants of childbearing potential
- Obtain blood samples for tests listed in Table 3
- Obtain urine sample for β-hCG pregnancy test for females of childbearing potential only
- Collect data from surveys including information on substance use and quality of life
- Adherence counseling
- Chart review of YRG-JHU ICC data to document HIV and antiretroviral therapy status and engagement in opioid substitution therapy (OST)

4a5.2. Treatment administration

Subjects in Arm 1 will be required to visit the Bilaspur ICC once weekly for four weeks. During these visits, participants in Arm 1 will receive their pegylated interferon alfa-2a shots subcutaneously at the clinic by a registered medical practitioner. They will be compensated INR 100 (USD 1.5) for these visits (since this is not the standard of care).

Subjects in Arms 1 and 2 will also receive 3 doses of SOF and DAC, which they will be instructed to take home and use as backup in case there is a problem receiving the daily medication from field workers. Otherwise, all doses of SOF and DAC will be delivered as directly observed therapy (DOT) daily in the field including Saturday and Sunday doses. Peer-health workers (PHW) (1 per 15-20 participants: total 4 for the study) will deliver the SOF and DAC via DOT on a daily basis to a location of the participant's choosing. We will provide the PHW with laptops/tablets that have a fingerprint reader to record the daily delivery of SOF and DAC and also to also ensure that the drugs are being delivered to the correct participant.

Subjects in Arm 3 will receive their first 4 weeks of treatment supply at baseline and two refills of 28 day's worth of doses at Weeks 4 and 8.

Dose Reduction
If a serious adverse reaction develops in Arm 1 participants during the course of treatment (See Section 8c), the dose of PEG will be modified according to standard guidelines until the AE abates or decreases in severity. See Table 1 for procedures related to depression and see Table 2 for procedures related to hematologic abnormalities. Selective serotonin reuptake inhibitors are available through government hospitals in India and will be made available to study subjects as needed. If persistent or recurrent serious adverse events develop despite adequate dosage adjustment, treatment will be discontinued.

Table 1. Procedures for Dose modification for serious adverse events related to depression

Depression Severity	Initial Management (4-8 weeks)		Depression		
	Dose modification	Visit Schedule	Remains stable	Improves	Worsens
Mild	No change	Evaluate once weekly by clinician at visit and daily recording of symptoms by outreach worker in field	Continue weekly visit schedule	Continue weekly visit schedule	(See moderate or severe depression)
Moderate	Decrease PEG dose 50%	Evaluate once weekly by clinician at visit and daily recording of symptoms by outreach worker in field	Consider psychiatric consultation. Continue reduced dosing.	If symptoms improve and are stable for 4 weeks, may resume normal visit schedule. Continue reduced dosing or return to normal dose.	(See severe depression)
Severe	Discontinue PEG permanently	Immediate psychiatric consult with CIMS	Psychiatric therapy as necessary as supervised by physician at CIMS		

Table 2. Procedures for Dose modification for serious adverse events related to hematologic abnormalities

Laboratory values		Pegylated Interferon α2a
Hgb	<10.0 g/ dl	---
	<8.5 g/dl	Permanently discontinue
WBC	<1.5 x 10^9/L	Reduce dose by 50%
	<1.0 x 10^9/L	Permanently discontinue
Neutrophil	<0.75 x 10^9/L	Reduce dose by 50%
	<0.5 x 10^9/L	Permanently discontinue
Platelets	<50 x 10^9/L	Reduce dose by 50%
	<25 x 10^9/L	Permanently discontinue
Bilirubin – direct	2.5 x ULN*	Permanently discontinue
Bilirubin – indirect	>5 mg/dl	
	>4 mg/dl (for 4 weeks)	Permanently discontinue
Creatinine	> 2 mg/dl	Permanently discontinue
ALT/AST	2 x baseline and 10 x ULN	Permanently discontinue

*ULN = upper limit of normal

Treatment interruption

We will track missed doses using our biometric system in Arms 1 ad 2. Participants who miss >1 but fewer than 2 weeks of doses will have their treatment extended so that they complete the total number of doses in their assigned arm (e.g., 28 for Arm 1 and 84 for Arm 2). If a client misses 2 weeks of more of therapy,

treatment will be restarted in its entirety at the discretion of the study physician and in consultation with the participant. Treatment can only be restarted one time. If there is a second interruption of >2 weeks, treatment will not be restarted. Participants in Arm 3 will be counseled to complete all doses of medications even if it takes longer than 84 days (e.g., 94 days). If participants in Arm 3 report an interruption >2 weeks at their 4-weekly medication refill visit, they will also be provided with one opportunity to restart treatment for the entire duration of 12 weeks at the discretion of the study clinician as with Arms 1 and 2.

4a5.3. End of Treatment Visit

The following procedures/assessments will be completed at the End of Treatment Visit

- Obtain vital signs
- Assessment of adverse events and concomitant medications
- Review medication compliance with subject. Subject should bring any missed doses to this visit.
- Obtain blood samples for sample storage in Table 3
- Brief survey on quality of life and alcohol and drug use
- Perform targeted physical examination
- Chart review of YRG-JHU ICC data to document HIV and antiretroviral therapy status and engagement in opioid substitution therapy (OST)

4a5.4. Early termination visit

Subjects discontinuing treatment prior to completion of the assigned dosing period will be asked to complete an Early Termination visit as described below. In addition, these subjects will be asked to complete the 12-week Post Treatment visit. Subjects with HCV RNA < lower limit of quantification (LLOQ) who permanently discontinue all study drugs for any reason including safety and/or tolerability concerns prior to completion of the assigned dosing period will be followed according to the post-treatment study assessments to determine whether the subject achieves SVR.

The Principal Investigator will be consulted prior to subject discontinuation when medically feasible. Study medication will be discontinued in the follow instances:

- Unacceptable toxicity, as defined in Section 8c of the protocol, or toxicity that, in the judgment of the study clinician and principal investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest
- Pregnancy in female participants
- Significant protocol violation including non-compliance with study assessments
- Subject requests to discontinue for any reason

The following procedures will be performed at the early termination visit.

- Perform targeted physical examination
- Obtain vital signs
- Obtain body weight
- Assessment of adverse events and concomitant medications
- Obtain blood samples for:
    - HCV RNA testing
    - Complete blood count
    - Liver function tests
    - Renal function tests
    - These samples will be used to estimate FIB-4 (stage fibrosis)
- Brief survey on quality of life and alcohol and drug use
- Subject should return all extra medication doses at this visit
- Chart review of YRG-JHU ICC data to document HIV and antiretroviral therapy status and engagement in opioid substitution therapy (OST)

4a5.5. 12-week post-treatment visit (Week 16 for Arm 1 and Week 24 for Arms 2 and 3)

The following procedures will be performed at the 12-week post treatment visit.

- Obtain vital signs
- Obtain body weight
- Obtain blood samples for laboratory tests listed in Table 3
- Brief survey on quality of life and alcohol and drug use
- Chart review of YRG-JHU ICC data to document HIV and antiretroviral therapy status and engagement in opioid substitution therapy (OST)

4a5.6. Additional details on laboratory tests and clinical assessments at visits.

Table 3. Schedule of assessments:

	Screening	Baseline/ Day 1	End of treatment****	SVR 12*****
HCV RNA	X			X
HIV*	X			
HBsAg*	X			
IL 28b		X		
Prothrombin time	X	X		
α fetoprotein	X			
TSH**	X			
CBC with diff**	X			X
LFT**	X			X
RFT**	X			X
Complete physical exam	X			
Targeted Physical Exam		X	X	
Sample Storage	X		X	X
Adherence assessment***			X	

*HIV and HBsAg will only be done if the subject has not been tested in the past 3 months
**TSH = Thyroid stimulating hormone; CBC = complete blood count; LFT = Liver function tests; RFT = Renal function tests
****at 5 weeks for Arm 1, 12 weeks for Arms 2 and 3
*****At 17 weeks for Arm 1, 24 weeks for Arms 2 and 3

HCV RNA will be assessed using the Abbott Realtime HCV assay and will quantify the number of copies of HCV RNA per milliliter (copies/ml). Complete blood count (CBC) will include hemoglobin, total white blood cell (WBC) count, total lymphocyte count, packed cell volume, total red blood cell (RBC) count, differential count, erythrocyte sedimentation rate, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and platelet count. Liver function tests (LFT) will include ALT, AST, total and direct bilirubin, total protein, serum albumin, serum globulin, albumin-globulin ratio, γ-GT and alkaline phosphatase. Renal function tests
(RFT) will include blood urea nitrogen and serum creatinine. Plasma will be processed and stored at -70° C for future testing.

Complete physical examination: A complete physical examination will include documentation of general appearance and examination of the following body systems: head, neck and thyroid; eyes, ears, nose, throat, mouth and tongue; chest (excluding breasts); respiratory; cardiovascular; lymph nodes, abdomen; skin, hair, nails; musculoskeletal; neurological.

Targeted physical examination: This exam will focus on signs and symptoms related to liver disease.

Retinal examination: A funduscopic retinal examination will be performed for those in Arm 1. This will be performed by the study doctor and the subject may be referred to a specialist if needed.

Vital signs: Assessment of vital signs will include measurement of resting blood pressure, pulse, respiratory rate and temperature.

Pregnancy testing: All females of childbearing potential will have a urine pregnancy test at the Screening and Baseline visits.

Survey: We will use the EuroQOL-5D as well as the WPAI: Hepatitis C Quality of Life Surveys. These will be translated into the local language. While these surveys are intended to be self-administered, low literacy rates in our population will require that they be interviewer administered. We will also include brief questions on frequency of drug and alcohol use.

Chart Review: The YRG-JHU ICC maintains an electronic database to monitor client visits, test results and service utilization. Data that are available through this database will be abstracted from these patient records rather than collected de novo. Specifically, we are interested in HIV status and whether participants are engaged in antiretroviral therapy and/or opioid substitution therapy.

b. Study duration and number of study visits required of research participants.

Participants in all Arms will have 4 study visits (Screening, Baseline, End of Treatment and SVR12). Participants in Arm 1 will have an additional 3 visits for interferon injections, and participants in Arm 3 will have an additional two visits to pick up medication refills. The duration of the study will be 16 weeks for Arm 1 and 24 weeks for Arms 2 and 3.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

This study will not be blinded. In part, this is so that clinicians can appropriately monitor for side effects associated with pegylated interferon alfa-2a. The regimens delivered require different forms of delivery (e.g., pegylated interferon is an injectable medicine) and for different durations of time making blinding not feasible.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

All participants will be able to receive the same routine medical care that they receive at the center and no other therapies will be stopped.

e. Justification for inclusion of a placebo or non-treatment group.

This study does not involve a placebo group.

f. Definition of treatment failure or participant removal criteria.

Treatment failure will be defined as HCV RNA>LLOQ (lower limit of quantification) at least 12 weeks after therapy has been completed. Participants who fail treatment will be referred to a government center clinic or their personal physician for follow-up – if participants fail therapy in Arm 1, they will be able to receive 12 weeks of SOF+DAC as is the standard of care.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Hepatitis C treatment is curative in a large proportion of those who complete a course of therapy. For those who achieve the desired treatment endpoint, sustained virologic response (HCV RNA <LLOQ 12 weeks after treatment is completed), no additional treatment will be needed. Those participants who fail treatment will be considered treatment failures and will be eligible to receive alternate regime.

5. Inclusion/Exclusion Criteria

All participants will be recruited from the Bilaspur ICC. Most of the inclusion/exclusion criteria are related to the use of pegylated interferon. Because we will be randomizing participants, all participants must satisfy the eligibility criteria for pegylated interferon. Our trial is restricted to non-cirrhotics because treatment of cirrhotics with SOF+DAC may require 24 weeks. Other pangenotypic regimens which can be given for 12 weeks such as sofosbuvir and velpatasvir are not yet available in India and so treating cirrhotics is beyond the scope of this study. We will use the FIB-4 to screen for potential cirrhosis. Anyone with a FIB-4>3.25 will be referred to the Medical Gastroenterology Department of CIMS for further assessment prior to treatment initiation. In cases where cirrhosis is ruled out after further investigation (e.g., imaging), potential participants can be rescreened for the study.

Inclusion criteria: Subjects must satisfy *all* of the following inclusion criteria listed below to be eligible for participation in this study:

1. Willing and able to provide written informed consent
2. Age ≥ 18 years
3. Documented evidence of chronic HCV infection (HCV RNA positive)
4. Participant is a resident of Bilaspur and can provide locator information that can be verified by one of the study staff
5. If participant is co-infected with HIV, he/she must have a CD4 > 350 cells/mm^3 and be either: 1) ART naïve or 2) on ART be on a tenofivir-containing regimen. If a subject's CD4 drops below 350 cells/μl (current threshold for HIV treatment in India), he/she will be able to initiate ART but we will ensure that the subject starts on a tenofivir-containing regimen, which is currently the standard for persons newly initiating ART in India.
6. Subjects must have the following laboratory parameters at screening:
    a. ALT ≤ 10 x the upper limit of normal (ULN)
    b. AST ≤ 10 x ULN
    c. Hemoglobin ≥ 10 g/dl for male and 9 g/dl for female subjects
    d. International normalized ratio (INR) ≤ 1.5 x ULN unless subject has known hemophilia or is stable on an anticoagulant regimen affecting INR
    e. Albumin ≥ 3 g/dl
    f. Direct bilirubin ≤ 1.5 x ULN
    g. Creatinine clearance ≥ 30 ml/min as calculated by the Cockcroft-Gault Equation
    h. Alpha fetoprotein < 50 ng/ml
    i. Absolute neutrophil count (ANC) ≥ 1,500/μL
    j. Platelets ≥ 90,000/μL
    k. Thyroid stimulating hormone (TSH) ≤ ULN
    l. FIB-4 ≤3.25 (Participants with a FIB-4 >3.25 will be referred to the medical gastroenterology department for further assessment for cirrhosis. If further assessment rules out cirrhosis participants can be rescreened for the study.
7. A female subject is eligible to enroll in the study if it is confirmed that she is:
    a. Not pregnant or nursing
    b. Not of childbearing potential (i.e., women who have had a hysterectomy, have both ovaries removed or medically documented ovarian failure, or are postmenopausal women > 50 years of age with cessation (for ≥12 months) of previously occurring menses)
    c. Of childbearing potential (i.e., women who have not had a hysterectomy, both ovaries removed or medically documented ovarian failure). [NOTE: Women ≤50 years of age with amenorrhea will be considered to be of childbearing potential.] These women must have a negative urine pregnancy test at screening and a negative urine pregnancy test on the Baseline /Day 1 visit prior to randomization and agree to one of the following modes of contraception for the duration of treatment and 12 weeks thereafter.
        - Complete abstinence from intercourse. Periodic abstinence (e.g., calendar, ovulation, sumptothermal, post-ovulation methods) is NOT permitted.

        or

i. Consistent and correct use of 1 of the following methods of birth control listed below in addition to a male partner who correctly uses a condom from 3 weeks prior to Baseline/Day 1 until the end of treatment. Women of childbearing potential must not rely on hormone-containing contraceptives as a form of birth control during the study. Female subjects using a hormone containing contraceptive prior to screening may continue their contraceptive regimen in addition to the study specified methods of birth control.

-intrauterine device (IUD) with a documented failure rate of less than 1% per year
-female barrier method: cervical cap or diaphragm with spermicidal agent
-tubal sterilization
-vasectomy in male partner

8. Subjects must be of generally good health as determined by the investigator.
9. Subjects must be able to comply with the dosing instructions for study drug administration and be willing to complete the study schedule of assessments.

Exclusion criteria: Subjects who meet *any* of the following exclusion criteria will not be enrolled in the study.

1. Pregnant or nursing female
2. Current or prior history of clinical hepatic decompensation (e.g., ascites, encephalopathy or variceal hemorrhage, MELD<12)
3. Prior treatment for hepatitis C virus infection
4. Infection with hepatitis B virus (HBsAg positive)
5. Chronic use of systematically administered immunosuppressive agents (e.g., prednisone equivalent >10 mg/day)
6. Use of any prohibited concomitant medications within 28 days of the Baseline/Day 1 visit.
7. Contraindications to PEG
8. Known hypersensitivity to the metabolites or formulation excipients of PEG (for Arm 1 subjects)
9. Active significant psychiatric condition(s) including severe depression, severe bipolar disorder and schizophrenia. Other psychiatric disorders are permitted if the condition is well controlled with a stable treatment regimen for ≥ 1 year from screening, or inactive for ≥ 1 year from screening.
10. Presence of autoimmune disorders (e.g., systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis, psoriasis of greater than mild severity)
11. History of clinical significant retinal disease
12. Clinical evidence of cirrhosis

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

From our previous work, the most prevalent HCV genotype among PWID in India is 3, followed by 1. The goal for resource limited settings is a pan-genotypic regimen that will not require expensive and specialized diagnostic tests such as HCV genotype testing.

SOF+DAC is an interferon-sparing regimen, making it attractive for use in RLS due to its optimal safety profile. SOF has been used in over a million persons globally with no clear side-effect patterns. While there are concerns about interferon use in general, the shorter duration of the PEG containing regimen (4 weeks) makes this regimen an attractive choice particularly among hard-to-reach populations for the following reasons. First, the shorter duration lends itself to a directly observed therapy (DOT) model of HCV treatment delivery, which could be integrated with programs such as opiate substitution therapy (OST) to maximize effectiveness. Second, while PEG has been associated with serious side effects, most of these side effects appear much later in therapy (>24 weeks); traditionally, PEG is used for ~48 weeks in the management of genotype 1 infection and most reports of adverse events and side effects of PEG arise from these ~48 week therapeutic courses. It is likely, therefore, that with 4 weeks of PEG, side effects will be minimal. In our prior pilot trial, we observed no serious adverse events with 12 weeks of PEG and no participants discontinued treatment due to side effects.

Details on the drugs to be used are below:

6a1. Sofosbuvir

Sofosbuvir (formerly PSI-7977) is a nucleotide analog that is a potent and selective inhibitor of NS5B-directed HCV replicon RNA replication in vitro and is intended for the treatment of chronic HCV infection.

Sofosbuvir, a prodrug of 2'-deoxy-2'-fluoro-2'-C-methyluridine monophosphate, is ultimately converted to the active uridine triphosphate form, GS-461203, within the hepatocyte. With either compound, systemic exposure to two metabolites (GS-566500 and GS-331007) accounts for the majority of the total systemic exposure in all species studied to date, including humans.

6a1.1. Description and Handling of Sofosbuvir

Formulation
Sofosbuvir tablets, 400 mg, are yellow, capsule-shaped, film-coated tablets debossed with "GSI" on one side and "7977" on the other side. In addition to the active ingredient, Sofosbuvir tablets contain the following inactive ingredients: mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, polyvinylalcohol, titanium dioxide, macrogol, talc, and iron oxide, yellow.

Packaging and Labeling
Sofosbuvir tablets are packaged in white, high density polyethylene (HDPE) bottles. Each bottle contains 30 tablets and a silica gel desiccant canister or sachet and polyester packing material. Each bottle is enclosed with a white, continuous thread, child-resistant screw cap with an induction-sealed, aluminum-faced liner.

Sofosbuvir bottles to be used will meet all applicable requirements of Good Manufacturing Practices: Manufacture of investigational medicinal products (July 2003) and the Drug Controller General India (DCGI).

Storage and Handling
Sofosbuvir will be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of Sofosbuvir and to ensure proper product identification, Sofosbuvir will not be stored in a container other than the container in which it is supplied. Consideration will be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions will be followed to avoid direct eye contact or exposure through inhalation when handling Sofosbuvir.

6a2. Daclatasvir

Daclatasvir is an inhibitor of HCV nonstructural protein 5A (NS5A). It is a direct-acting antiviral agent (DAA) against the Hepatitis C virus.

Daclatasvir binds to the N-terminus of NS5A and inhibits both viral RNA replication and virion assembly. Characterization of Daclatasvir-resistant viruses, biochemical studies, and computer modeling data indicate that Daclatasvir interacts with the N-terminus within Domain 1 of the protein, which may cause structural distortions that interfere with NS5A functions.

6a2.1. Description and Handling

Formulation
Daclatasvir tablets are light green, biconvex, and pentagonal-shaped, debossed with “BMS” on one side and “215” on the other side. Daclatasvir 60 mg tablets contain 60 mg daclatasvir (equivalent to 66 mg daclatasvir dihydrochloride) and the inactive ingredients anhydrous lactose (116 mg), microcrystalline cellulose, croscarmellose sodium, silicon dioxide, magnesium stearate, and Opadry green.

Packaging and Labeling
Each bottle contains 28 tablets.

Daclatasvir bottles to be used will meet all applicable requirements of Good Manufacturing Practices: Manufacture of investigational medicinal products (July 2003) and the Drug Controller General India (DCGI).

Storage and Handling
Daclatasvir will be stored in a securely locked area, accessible only to authorized site personnel. To ensure the stability of Daclatasvir and to ensure proper product identification, Daclatasvir will not be stored in a container other than the container in which it is supplied. Consideration will be given to handling, preparation, and disposal through measures that minimize drug contact with the body. Appropriate precautions will be followed to avoid direct eye contact or exposure through inhalation when handling Daclatasvir.

6a3. Peglyated-interferon alfa-2a

Peglyated-interferon alfa-2a (PEG) is composed of a recombinant interferon alfa-2a covalently bound to a 40 kDa branched polyethylene glycol molecule. Peglyated-interferon alfa-2a has a decreased systemic clearance rate and a rapid but sustained absorption and circulates in the blood much longer than does the parent interferon alfa-2a compound, resulting in a longer half-life (80 hours), and enabling weekly dosing.

Interferons elicit an immune response upon binding to cell surface receptors, triggering expression of numerous interferon-responsive genes. Among the proteins produced by interferon activation are those that break down and destabilize viral RNA (RNases) and inhibit viral protein translation. Interferon also stimulates cell-mediate immunity by promoting memory T-cell, natural killer cells, and dendritic cell activation and/or proliferation. A comprehensive review of PEG is contained in the package insert/SmPC.

6a3.1. Description and Handling
Formulation
Peglyated-interferon alfa-2a is commercially available as Taspiance by Emcure Pharmaceuticals in India and will be provided in this study as 180 µg/0.5 mL pre-filled syringes. Each syringe is to deliver 0.5 mL of drug product. The formulation, which is subcutaneously administered, contains sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate trihydrate, acetic acid, and water for injection. The solution is colorless to light yellow and the pH is 6.0 ± 0.5.

Packaging and Labeling
The PEG will meet all applicable requirements of Good Manufacturing Practices: Manufacture of

investigational medicinal products (July 2003) and the Drug Controller General India (DCGI).

Storage and Handling
Peglyated-interferon alfa-2a prefilled syringes will be stored in the refrigerator at 2 °C to 8 °C (36 °F to 46 °F) protected from light and will not be frozen or shaken. Syringes are for single use only.

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

N/A

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

N/A

7. Study Statistics

a. Primary outcome variable.

The primary outcome will be sustained virologic response (SVR12), which is defined as HCV RNA < lower limit of quantification 12 weeks after treatment completion.

b. Secondary outcome variables.

Adherence for comparison across the three arms will be defined using a combination of the biometric data for Arms 1 and 2 and self-report and pill counts for Arm 3. Serious adverse events requiring dose modification or treatment discontinuation will include primarily laboratory abnormalities including anemia, neutropenia and thrombocytopenia. For any adverse event outcome, we will consider occurrence of any of the side effects commonly associated with treatment with pegylated interferon alfa-2a, including but not limited to fatigue, headache, pyrexia, myalgia, rigors, insomnia, nausea, alopecia, irritability, arthralgia, anorexia, dermatitis, depression, or fatigue.

c. Statistical plan including sample size justification and interim data analysis.

All analyses will be conducted as intention to treat. We will use a chi-squared test of proportions to compare the proportions that achieve SVR12. Pairwise comparisons with correction for multiple comparisons will be conducted to directly compare Arms 1 and 2, Arms 1 and 3 and Arms 2 and 3. For secondary outcomes, chi squared tests of proportions will be used to compare categorical outcomes and a Wilcoxon rank-sum test will be used to compare adherence.

The primary objective of this study is to test the feasibility of DOT for HCV treatment among HCV-infected persons with substance use history in a resource limited setting. An additional objective is to generate pilot data to plan a larger powered study. We hypothesize that SVR12 will be higher in Arm 1 compared to Arms 2 and 3. Assuming a two-sided alpha=0.05, 50 people in each arm and 70% achieving SVR12 in Arm 3, we will have >80% power to detect a difference of 25% (e.g., 95% completion in the SOF+DAC+PEG).

No interim analyses will be conducted as with 150 participants, it will not be possible to observe statistical differences prior to the completion of the trial.

d. Early stopping rules.

As we do not plan to do interim analyses, the only reason for stopping the trial would be a higher frequency than expected of serious adverse events. We will continually monitor the frequency of serious adverse events and if this frequency is 10% or higher, we will prematurely stop the trial.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

It is anticipated that most participants who complete their full course of treatment with optimal adherence will clear hepatitis C from their bodies. However, for those individuals who do not respond to treatment, it is possible that non-response will affect their ability to respond to other drugs for hepatitis C in the future. However, with the newer direct acting antiviral (DAA) regimens, response rates have been demonstrated to be comparable in treatment naïve and prior non-responders. The primary risk related to taking these medications is with respect to side effects associated with pegylated interferon alfa2a.

It is anticipated that the majority of side effects will be related to pegylated interferon as side effects associated with SOF and DAC are rare. With pegylated interferon, the side effects most commonly reported that are of concern include depression, suicidal thoughts, relapse of drug use by former drug users and bacterial infections complicated or made possible by low white blood cell counts. Notably, previously pegylated interferon has primarily been used as part of 48-week regimens and the majority of the side effects occurred beyond 20-24 weeks of therapy, so we anticipate that the frequency of side effects in our study participants will be lower than what has been observed with longer regimens.

Because we will be delivering daily doses of SOF and DAC for Arm 1 and 2 participants in the field, there are additional risks related to disclosure of a participants' HCV status through the receipt of this medication every day from a field worker.

b. Steps taken to minimize the risks.

Procedures to minimize risk include carefully training personnel 1) to be competent in venipuncture; 2) to recognize and address psychological issues; and 3) to maintain confidentiality. Psychological risks are minimized by the availability of trained counselors in the study clinic. If further assistance is needed, we will have access to the psychiatry department at CIMS. The study clinicians are also trained in CPR as part of medical education in India. Abnormal clinical findings and/or laboratory values will be conveyed in a timely manner to the participants and, with the consent of the subject, form the basis of a facilitated referral to a hospital, clinic, or a physician of the subject's choosing. Subjects who continue to report active drug and alcohol use will be offered individual counseling and referral for treatment of their drug use or alcohol use, should they request one. All participants will receive risk reduction counseling (including the importance of abstaining from alcohol use) at each visit after data collection is completed and prior to scheduling subsequent study visits. This intervention will make our cohort somewhat different from the general population of PWID, but it is useful to provide lower bounds of counseling. We have established cooperation with several drug abuse treatment organizations and this may help facilitate personalized facilitated referrals.

Safeguards will also be taken to ensure that subjects' confidentiality is maintained. These measures include: 1) unique study numbers in databases and on specimens; 2) maintaining identifiers separately in a password protected database (utilizing two levels of password security); 3) restricting access to locked files and password protected databases to essential study personnel. All data will be reported in aggregate form only without personal identifiers. In the case of an adverse event, policies and procedures are in place to work with the subject and to keep the study's governing bodies informed

The study doctor and study staff will monitor participants for any signs of new or unexpected side effects at weekly study visits for Arm 1 and during daily visits in the field for Arms 1 and 2. Participants will be informed to contact the study doctor if they have side effects or are unable to perform daily functions. They will be given contact phone numbers and a means to SMS outreach workers in order to report side effects. In addition, the field workers who will be delivering SOF and DAC in the field will be trained to ask questions about side effects to capture any potential problems in real time. A detailed list of potential side effects and their relative frequency will be included on the consent form.

Our study team, including our doctors and outreach workers, has been working with drug users for the past 3

years and has extensive experience in delivering HIV care. They will receive training from physicians at the Johns Hopkins Viral Hepatitis Clinic who have been treating hepatitis C for 20 years and the team at YRGCARE in Chennai who have been treating HCV for the past 5 years. They will be trained to look for and manage all potential adverse effects of therapy and will have the ability to receive guidance from experts from the Johns Hopkins Viral Hepatitis Clinic (Mark Sulkowski). Through Centers for Disease Control funding, a new Maryland Community-Based Program To Test and Cure Hepatitis C has been established. Administered by the Maryland Department of Health and Mental Hygiene (DHMH) in collaboration with a coalition of clinical and public health partners, this initiative will strengthen healthcare capacity to diagnose and cure HCV infection through the implementation of a clinician training and on-going telemedicine program. The clinician training and telemedicine program will be implemented by the Division of Infectious Diseases at Johns Hopkins University (JHU), a national leader in viral hepatitis management. Through its Viral Hepatitis Center (VHC), JHU will train clinicians to effectively test for HCV and offer appropriate treatment. As part of this training program, clinicians at our site in India will have access to weekly video conferences, which include provider clinical case consultations and co-management of cases as well as on call- 24 hour clinical consultations.

Female participants will be guided to exercise care to avoid pregnancy in female subjects. Women of childbearing potential will be required to use effective methods of birth control. The study doctor will document what type(s) of birth control are being used. Participants will be given strict instructions about what to do if they become pregnant during the course of the study.

Finally, field workers will be trained to exercise discretion when delivering SOF and DAC in the field. The daily meeting will occur at a place, which the participant chooses and the field worker will not identify as being a part of a study nor with anything related to injection drug use or hepatitis C. Most of the field workers employed are former drug users and hence, have an excellent rapport with the study community and have experience in reaching PWID in the field as part of the YRG-JHU ICC study.

c. Plan for reporting unanticipated problems or study deviations.

8c1. Adverse Events (AE)

An AE is any untoward medical occurrence in a clinical investigation subject administered medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs also include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure (e.g., venipuncture) during or after screening (before the administration of study investigational medicinal product)
- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study investigational medicinal product phase of a human clinical trial will also be considered an AE.
- Complications and termination of pregnancy
- All AEs that occur from the study screening visit onwards and throughout the duration of the study, including the follow-up off study medication period will be recorded as an AE.

An AE does not include the following

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed; the condition that leads to the procedure is an adverse event.
- Pre-existing disesase or conditions or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)
- Overdose without clinical sequelae

- Any medical condition or clinically significant laboratory abnormality with an onsent date before the consent form is signed and not related to a protocol-associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history form.
- Uncomplicated pregnancy
- An induced elective abortion to terminate a pregnancy without a medical reason

8c1.1. Assessment of Adverse Events

All AEs will be assessed by the principal investigator or qualified designee (Study Doctor) and recored on the AE form. The AE entry will indicate whether or not the AE was serious, the start date (AE onset), the stop date (date of AE resolution), whether or not the AE was related to study drug or a study procedure, the action taken with the study drug due to the AE and the severity of the AE. The principal investigator will be resonsible for final review and confirmation of accuracy of events, relationship and severity confirmed by signature on the AE form.

The relationship to the study drug will be assessed using a combination of clinical judgement and the following considerations:

- NO: Evidence exists that the adverse event has an etiology other than the study drug. For serious adverse events, an alternative causality will be provided (e.g., pre-existing condition, underlying disease, intercurrent illness or concomittant medication).
- YES: There is a resonable possibility that the event must have been caused by the investgiational medicinal product.

It should be emphasized that ineffective treatment should not be considered as causally related in the context of AE reporting.

The relationship to study procedures (e.g., invasive procedures such as venipuncture or biopsy) should be assessed using the following considerations:

- NO: Evidence exists that the AE has an etiology other than the study procedure.
- YES: The AE occurred as a result of protocol-mandated procedures such as venipuncture.

The severity grading of AEs will be assessed as Grade 1, 2, 3 or 4 using a standard grading scale for severity of adverse events and laboratory abnormalities. This has been adapted from those used for Industry sponsored trials in the US. For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

<u>8c2. Serious Adverse Events</u>

A **serious adverse event (SAE)** is defined as follows:

Any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening situation (subject is at **<u>immediate</u>** risk of death)
- In-patient hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other SAEs)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received investigational medicinal product
- Other medically significant events that may not be immediately life-threatening or result in death or hospitalization, but based upon appropriate medical and scientific judgement, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Examples of such events are as follows:

- Intensive treatment in an emergency room or at home for an allergic bronchospasm
- Blood dyscrasias or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

8c2.1. Classification of Serious Adverse Events (SAEs)

- Death is an outcome of an AE, and not an adverse event in itself. In reports of death due to "Disease Progression," where no other information is provided, the death will be assumed to have resulted from progression of the disease being treated with the study drug.
- The subject may not have been on the study drug at the occurrence of the event. Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE.
- "In-patient hopsitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.
- The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

A distinction should be drawn between the seriousness and the severity of the AEs. An AE that is assessed as Grade 4 (potentially life-threatening) should not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as Grade 4. An event is defined as "serious" when it meets one of the predefined outcomes described above.

All SAEs will be recorded on the Serious Adverse Event report form and submitted within 24 hours of the principal investigator's knowledge to both the US and the YRGCARE IRBs. For fatal or life-threatening SAEs, we will also include hospital case reports, autopsy reports or other hospital documents when applicable.

The principal investigator will take all therapeutic measures necessary for resolution of the SAE. Any medications necessary for treatment of the SAE will be recorded on the SAE form.

Follow-up of AEs will continue through the last day on study (including follow-up off-study medication period of the study) and/or until a conclusive outcome (e.g., resolved, resolved with sequelae, lost-to-follow-up, fatal) is achieved.

Participants who develop an SAE will be referred to the appropriate department within the Chattisgarh Institute for Medical Sciences (CIMS) as the ICC is on the campus of CIMS. This is a multi-specialty hospital, which has experts in medical gastroenterology, cardiology, nephrology, psychiatry, and urology among other specialties. Services available at CIMS are accessible by all YRGCARE patients and so we will use CIMS to manage all adverse events that cannot be managed directly at YRGCARE.

If a participant is injured as a result of being in this study, they will be given immediate treatment for injuries as per the standard of care at CIMS. The entire cost of health care and compensation due to study related injury or death will be taken care of by YRGCARE as per the order of the Licensing Authority in India (Drug Controller General India). This includes free medical management for as long as required and compensation to the family in the event of death. This is in compliance with the order specified in "Rule 122 DAB of the Drugs and Cosmetics Rules, 1945" and as per the Order from the Central Drugs Standard Control Organization.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

Legal and social risks are possible in that study participants are PWID who engage in illegal activities. However, we will take multiple precautions to protect against breaches of confidentiality. No identifying information will be included in the electronic data capture methods. Interviewers will be trained to not discuss the participants of the study. Results will be reported in aggregate form only.

e. Financial risks to the participants.

N/A

9. Benefits

a. Description of the probable benefits for the participant and for society.

While there is no guarantee that there will be any personal benefit from participating in this study, it is highly likely that both the regimens (SOF+DAC+PEG for 4 weeks and SOF+DAC for 12 weeks) will be efficacious in curing hepatitis C in a large percentage of the participants. This means that a participant will have no detectable HCV RNA and will be at a lower risk for developing long-term complications of hepatitis C including hepatocellular carcinoma. There is also societal benefit in terms of providing evidence that PWID can be treated with these medications in India. This may lead to further efforts to promote access to hepatitis C therapies in this population. In addition, participants will have close medical monitoring of their health condition by blood tests and other evaluations during clinic visits.

In addition to the primary aims of the study, this study will serve as a platform for other related investigations among this understudied population. Demonstrating that PWID in India can be treated for hepatitis C will be critical for future efforts to expand hepatitis C treatment access among PWID populations in India and elsewhere in resource-limited settings (RLS). To date, there have been few efforts to treat hepatitis C in this vulnerable population, particularly in RLS. Moreover, it is expected that by curing individuals in the community of their hepatitis C, the risk of HCV transmission will go down. Ultimately, it is our goal that these studies should help reduce morbidity and mortality among PWID in India and Asia, where similar conditions are prevalent.

10. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

Compensation for study visits will be the same for the three arms. Compensation is for travel to the study clinic and time spent in the clinic. Compensation will be for screening, baseline, end of treatment and the SVR12 visit. We will pay 300 INR (USD 4.7) for each study visit. In addition, the participants in Arm 1 will receive an additional 100 rupees at each visit to the ICC to receive their PEG injection. This is to compensate their travel time to the ICC. Thus, the total possible compensation for Arm 1 is INR 1500 and for Arms 2 and 3 is 1200 INR.

There is no penalty or consequence for not completing all of the phases of research. It will be made clear to participants that if they withdraw from the study early, it will not affect the care that they receive from the ICC, CIMS or other related facility. Moreover, if participants withdraw from the pilot study it will not affect their ability to receive services at our integrated care centre.

11. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There will be no costs to the study participants. All travel costs will be covered by the reimbursement and all costs for treatment and clinical monitoring will be covered by the study.