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Rationale and design of a randomized pragmatic trial of patient-centered models of hepatitis C treatment for people who inject drugs: The HERO study

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ABSTRACT

Background: Although people who inject drugs (PWID) having the highest incidence and prevalence of hepatitis C virus (HCV) in the US, HCV treatment is rarely provided to PWID due to assumptions about poor adherence and reinfection risk. As direct-acting antiviral agents (DAAs) have achieved sustained virologic response (SVR) rates of 95% or more, evidence-based strategies are urgently needed to demonstrate real-world effectiveness in marginalized patient populations such as PWID. The objectives of this study are: 1) to determine whether either of two patient-centered treatment models – patient navigation (PN) or modified directly observed therapy (mDOT) – results in more forward movement along the HCV care cascade including treatment initiation, adherence, and SVR; 2) using quantitative and qualitative methods, to understand factors associated with lack of treatment uptake, poor adherence (< 80%), failure to achieve SVR, DAA resistance, and HCV reinfection.

Methods: The HERO study is a multi-site, pragmatic randomized clinical trial conducted in eight states where 754 HCV-infected PWID were randomly assigned to either PN or mDOT.

Conclusions: This study addresses an urgent need for timely and accurate information on optimal models of care to promote HCV treatment initiation, adherence, treatment completion and SVR among PWID, as well as rates and factors associated with reinfection and resistance after treatment. This clinical trial has the potential to provide valuable information on how to reduce the burden of the HCV epidemic in PWID.

1. Introduction

Chronic hepatitis C virus (HCV) infection is one of the leading causes of morbidity and mortality in the US [1]. The prevalence of HCV infection is a growing burden that rose by 133% from 2004 to 2014 [2], mainly due to the growing epidemic of injection drug use (IDU) and the

Abbreviations: HCV, Hepatitis C virus; CHC, Community health centers; DAA, Direct-acting antiviral agents; IDU, Injection drug use; HERO, Hepatitis C Real Options; mDOT, Modified directly-observed therapy; OTP, Opioid treatment program; PN, Patient navigation; PWID, People who inject drugs; SVR, Sustained virologic response

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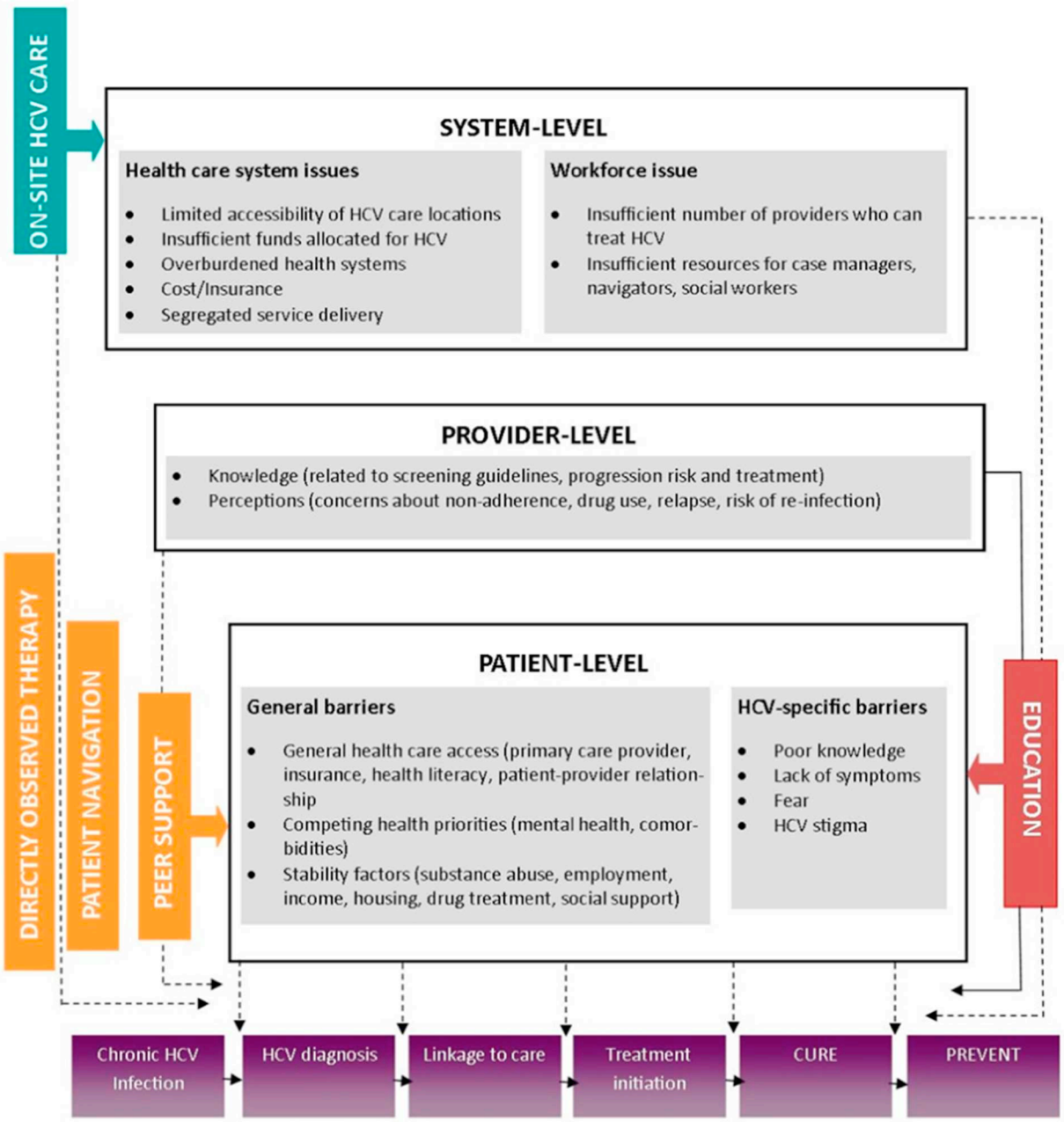

Fig. 1. Barriers to treatment.

opioid crisis. The highest prevalence of HCV infection is found among people who inject drugs (PWID), which has been estimated to be up to 77% [3]. Facilitating access to curative HCV treatment in PWID is an urgent public health priority [4]. Guidelines from the American Association for the Study of Liver Diseases (AASLD), Infectious Diseases Society of America (IDSA), European Association for the Study of the Liver (EASL), International Network of Hepatitis in Substance Users (INHSU), and the World Health Organization (WHO), recommend treatment for HCV infection among PWID [5–8]. It is estimated that treatment scale-up among PWID could reduce HCV prevalence by up to 75% within 15 years [9]. Unfortunately, HCV treatment uptake is extremely low among PWID (1-2%) [10].

Multiple interrelated barriers exist to direct-acting antiviral agent (DAA) treatment among PWID (Fig. 1). At the patient level, these may include general barriers, such as difficulties in accessing health care (e.g., lack of care provider), competing comorbidities (e.g., mental health), and stability factors (e.g., unemployment, homelessness), and HCV-specific barriers, such as limited knowledge of treatment and lack of symptoms [11–15]. At the provider level, barriers relate to provider concerns of ongoing substance use leading to poor adherence and re-infection [15–17]. Finally, system-level barriers can be related to the health care system, such as the price of the medications, insurance restrictions on prescribing DAAs especially to active drug users, and insufficient locations for HCV testing and treatment [17,18], and to workforce issues, such as an inadequate supply of HCV treatment providers [19].

As DAAs have achieved sustained virologic response (SVR) rates of ≥95%, evidence-based strategies are urgently needed to demonstrate real-world effectiveness among PWID. Multidisciplinary approaches that combine antiviral and addiction treatment have shown comparable rates of treatment uptake and SVR among PWID compared to non-PWID populations [20–26]. Similarly, interventions based in primary care settings have demonstrated that patients with ongoing drug use and psychiatric comorbidity can be effectively linked to HCV care

[12,27–31]. Peer-driven interventions including weekly support groups and patient navigation have also demonstrated high treatment uptake and SVR rates among PWID [32–34]. A modified directly-observed therapy (DOT) approaches have successfully supported HCV treatment in opioid agonist treatment programs [21,23,35], prison settings [36], and community health centers [32-33].

This report describes the HERO Study: Hepatitis C Real Options, a randomized pragmatic trial aimed at determining which model provides better HCV outcomes among PWID while also exploring which model is preferred by PWID. The study objectives are: 1) determining which of two patient-centered treatment models (patient navigation (PN) or modified directly observed therapy (mDOT)) results in greater treatment initiation, adherence and SVR; and 2) determining the incidence and factors associated with lack of treatment initiation, poor adherence, failure to achieve SVR, drug resistance, and HCV reinfection, using both quantitative and qualitative methods.

2. Methods

2.1. Study design

The HERO Study is a multi-site pragmatic clinical trial conducted in eight states, where 754 HCV-infected PWID who injected any illicit substances within 90 days of screening were randomized to either PN or mDOT. Quantitative data were collected from 1) participant interviews; 2) blood specimens for HCV viral load and resistance assays; 3) urine toxicology tests at research visits; 4) electronic pill packages for assessing adherence; and 5) clinic records for methadone or buprenorphine dose, clinical tests and medical history. Qualitative data on study implementation and outcomes were collected from patient, research team and staff interviews.

2.2. Study objectives

The primary objective is to determine whether SVR, defined as the absence of HCV ribonucleic acid (RNA) in the blood 12 weeks following the completion of treatment, is higher among PWID randomized to PN or those randomized to mDOT. The secondary objectives are to examine the following outcomes overall and by arm: 1) treatment initiation within 12 weeks of enrollment; 2) longitudinal biweekly adherence rates of prescribed medication measured using electronic Med-ic® blister packs; 3) treatment completion defined as finishing 100% of the prescribed 12-week course regardless of adherence to the medication; 4) the proportion who develop drug resistance; and 5) reinfection, defined as the rate (incidence) and the proportion who become HCV-infected 3 years after treatment completion.

2.3. Study setting

The study is being conducted in sites across eight states: New York City (NY), Providence (RI), Albuquerque (NM), San Francisco (CA), Boston (MA), Baltimore (MD), Seattle (WA), and Morgantown (WV), in eight opioid treatment programs (OTPs) that provide opioid agonist treatment (including methadone and buprenorphine) and 15 community health centers (CHCs). It is estimated that these OTPs provide care for 5000 HCV-infected patients and the CHCs provide care for 10,000 HCV-infected patients. The study is directed from Clemson University (SC).

2.4. Eligibility criteria

Eligibility criteria include: 1) age 18–70 years; 2) HCV viremia; 3) aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelets measured within the past 12 months; 4) self-report of actively injecting any substance within 90 days of screening; 5) not previously treated with HCV DAAs; 6) willing to receive treatment with sofosbuvir/velpatasvir; 7) willing to be randomized to PN or mDOT; 8) if receiving methadone treatment for opioid use disorder, then attending or willing to attend that program a minimum of 5 times per week if randomized to mDOT; 9) able to provide written informed consent; and 10) fluent in English or Spanish. Participants are excluded if 1) they are pregnant or breastfeeding, or 2) have been previously diagnosed with hepatocellular carcinoma. Co-infection with Human Immunodeficiency Virus (HIV) or hepatitis B is permitted, as is a diagnosis of compensated cirrhosis.

2.5. Approvals, confidentiality, and data safety and monitoring

The trial protocol was reviewed and approved by the Institutional Review Boards (IRB) of the 10 participating institutions: Clemson University/Prisma Health, Harvard School of Medicine/Massachusetts General Hospital, Albert Einstein College of Medicine/Montefiore Medical Center, Johns Hopkins University, University of Rhode Island, Partners Health Care, West Virginia University, University of California at San Francisco, University of New Mexico Health Sciences Center, and University of Washington. Written informed consent is obtained from all participants. A certificate of confidentiality was obtained by each site from the National Institutes of Health (NIH) to protect participants from being identified in any social, civil, criminal, or legislative dealings at the local, state, or federal level.

The principal investigator (PI), A.H.L., is responsible for monitoring the safety and efficacy of this study, executing the Data and Safety Monitoring (DSM) plan, and complying with all reporting requirements. The PI provides a summary of the DSM report to Patient-Centered Outcomes Research Institute (PCORI) on an annual basis as part of the progress report. Because the intervention is low risk and is integrated within usual clinical care, the main element of the monitoring plan is continuous, close monitoring by study staff and investigators, with prompt identification and reporting of serious adverse events (SAEs).

Each site maintains appropriate medical and research records in compliance with the International Council for Harmonization (ICH) of Technical Requirements for Pharmaceutical for Human Use E6, Section 4.9, and regulatory and institutional requirements for the protection of subject confidentiality. Forms for use as source documents are derived from the electronic case report forms (eCRFs) provided by the University of New Mexico Health Sciences Center Statistical and Data Coordinating Center (SDCC). Source documents are only accessible by study staff and all research records are kept in a locked file cabinet in a locked research office at each site.

2.6. Stakeholder engagement

Each of the eight enrolling research sites formed a Local Stakeholder Advisory Board (LSAB) which consists of a site PI, site Project Director (PD), patients, local advocacy organizations, and local representatives from participating venues such as OTPs and CHCs. During the course of the study, the LSAB meets on a quarterly basis to discuss study implementation, recruitment, participant tracking, intervention delivery, outcome assessment, and dissemination.

At a national level, a National Stakeholder Advisory Board (NSAB) was created. The NSAB consists of the site PIs, a local representative of each site, and representatives from governmental organizations; professional policy, educational, and advocacy organizations; professional patient organizations; and industry. The NSAB meets on a quarterly basis through the duration of the study to review outcomes related to the study implementation, progress, and dissemination.

2.7. Recruitment, enrollment, and reimbursement

Potential participants are identified through chart reviews of existing patients at the clinics, community-based outreach, and medical provider referrals. Participants are screened to see if they meet basic

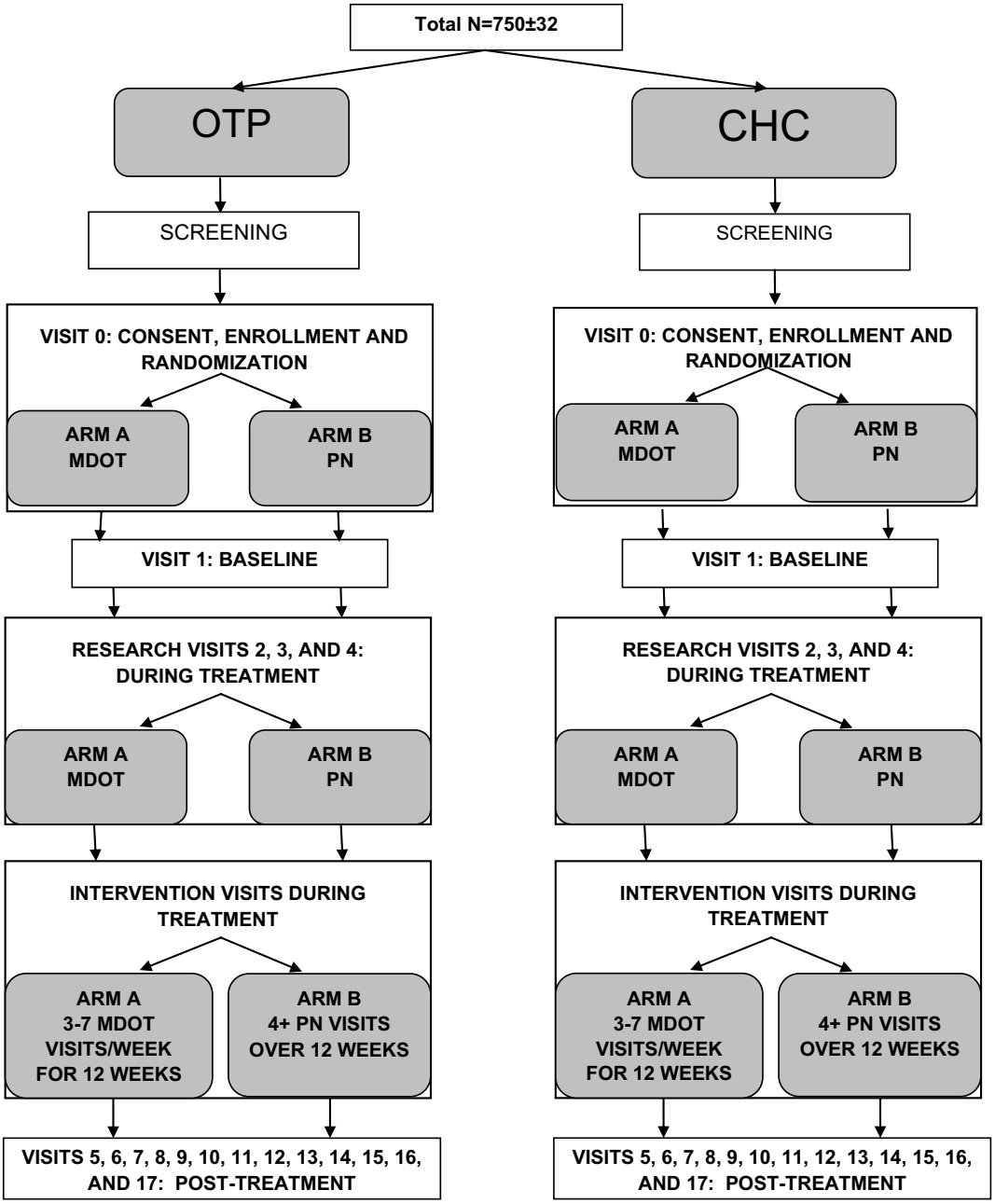

Fig. 2. Schematic of the study design.
Note: OTP: opioid treatment program; CHC: community health center; MDOT: modified directly-observed therapy; PN: patient navigation.

eligibility criteria and are asked if they are currently seeing a healthcare provider. If they have a provider, a release of information to view clinical records is obtained, data to assess eligibility are extracted, and study eligibility is documented on the electronic case report forms (eCRF). If they do not have a provider, they are referred to one at the CHC or OTP (if also interested in opioid agonist treatment) prior to obtaining a release of information for clinical records. Following chart review to assess study eligibility, a research staff member meets with the potential participant to confirm eligibility, discuss study procedures including randomization to the mDOT or PN interventions, risks and benefits of participation, and to obtain written informed consent. Eligible participants are enrolled within 1 month of screening. If enrollment did not occur within 1 month, eligibility is reassessed.

Participants are reimbursed $20 for the time and effort to attend each of 17 research visits and an additional $5 for returning weekly electronic blister packs for a total of $400 per participant over the course of the study. Participants are followed for 168 weeks. Enrollment commenced in September 2016, and treatment initiation began in October 2016. Enrollment concluded in August 2018, and the trial is expected to be completed in 2022.

2.8. Randomization

Seven hundred and fifty-four patients were enrolled, with patients randomized to PN or mDOT in a 1:1 ratio in variable block sizes of 2–6 via central, computer-generated randomization provided by the SDCC (Fig. 2). Randomization occurred in blocks to ensure comparison groups of approximately equal size. As the interventions are not blinded, block size will vary to prevent anticipation of treatment arm assignment.

Two randomization strategies (stratification and blocking) are used to avert imbalances in prognostic factors or treatment settings, and to

ensure comparison groups of approximately equal size. Participants are stratified by 3 factors: city, OTP vs. CHC, and stage of liver disease (cirrhosis vs. no cirrhosis).

To ensure a balance at the end of the trial in the primary analytic sample sizes of participants who initiated the HCV treatment between the PN and mDOT arms, an adaptive re-weighting of random allocation in a pseudo urn randomization fashion [37] will be applied. As we hypothesize that the number of randomized subjects who will initiate HCV treatment will be greater in the PN arm, adjustment of random allocation ratio for a potential imbalance between the arms will be made based on the observed allocation rates at the middle of the trial, i.e., when 300 participants had initiated treatment. If the observed difference is > 5% (i.e. < 47.5% vs. 52.5%) between the two arms, we will accordingly re-weight the 1:1 random allocation so that final sample sizes will be balanced. Of note, a randomized subject will not necessarily be a clinical treatment subject but will be included in the comparison of treatment initiation.

2.9. Baseline visit

The baseline visit occurs within 2 weeks of enrollment and prior to treatment initiation. Several different factors, including HCV clinical factors and psychosocial factors hypothesized to predict treatment initiation, adherence and treatment completion, are assessed using the following instruments: Modified Addiction Severity Index (ASI) – Baseline (drug use) [38] [38], Behavior Risk Assessment (injection behaviors) [39], Alcohol Use Disorders Identification Test (AUDIT-C, alcohol use) [38] [40], Substance Use Treatment (past and present experience with treatment), Patient Health Questionnaire (PHQ-9, depression) [39] [41], Generalized Anxiety Disorder Assessment (GAD-7, anxiety) [40] [42], EuroQOL five dimensions questionnaire (EQ-5D, quality of life) [41] [43], Stigma scale [44], Shame scale [45], Health efficacy, and Medical Outcomes Social Support Scale [46] (Table 1). Survey results are captured in REDCap, a secure, HIPAA-compliant web application for building and managing online surveys and databases. Participants provide a urine sample and blood is drawn. Counseling on avoidance of HCV transmission and HIV infection is provided, as well as information on local drug treatment, syringe services programs, and other referrals as needed. After all baseline instruments have been administered, research staff reveal the treatment delivery arm to which the participant has been randomized.

2.10. Study medication

Medications are dispensed in Med-ic® blister packs (Information Mediary Corp., Otawa, Canada). These electronic blister packs have a fine wire that is disrupted when the medication is removed and the circuit records the precise time and date of the removal, permitting assessment of adherence.

2.11. Interventions: mDOT vs. PN

2.11.1. mDOT

2.11.1.1. mDOT in the OTP clinics. This intervention is considered a modified version of DOT as observation of dosing is not daily. Participants in the mDOT arm receive: 1) five to seven directly observed doses per week at the same time as they receive methadone or buprenorphine, 2) individually packaged take-home doses for self-administration on weekends at the discretion of the OTP, and 3) two rescue doses to be used in the event they cannot attend the OTP. Since mDOT is linked to OTP visits, the number of directly observed oral doses varies based on the number of days the participant attends the clinic to receive directly observed methadone or buprenorphine.

2.11.1.2. mDOT in the CHC. Participants are offered mDOT via the mobile health app miDOT (developed by emocha Mobile Health, Inc., Baltimore, MD) to document study drug administration on a smartphone. All 7 doses a week are observed through submission of videos via the app. Participants are either provided with a smartphone that is pre-loaded with a data/min plan and the mDOT app, or download the mDOT app to their own smartphone. Research staff train the participant on how to use the app. Participants record a video of themselves taking their HCV medication, then upload the video to the database maintained by emocha. Staff review these videos within 72 h to confirm the participant took their medication. This intervention is still considered mDOT since doses are not necessarily observed by study staff on the same day doses are taken. Subjects using the mobile health app miDOT receive seven doses of medication on a weekly basis at their CHC. Subjects who decline the app are offered DOT in the health center and receive: 1) three to five directly observed doses in the health center or affiliated organization administered by staff, and 2) individually packaged take-home doses for self-administration on weekends and other clinic days.

2.11.2. PN

The study follows a PN model developed by the New York City Department of Health (NYDOH) in collaboration with Montefiore Medical Center and the community [43,44] [47,48]. HCV patient navigators assist with: 1) coordination of treatment, 2) health education and promotion, 3) overcoming barriers, and 4) psychosocial support. Details of the PN protocol and materials are documented in a patient navigator manual.

Study medication is packaged in Med-ic® blister packs and dispensed as a 2-week supply every other week. If the participant has difficulty on the biweekly schedule, the healthcare provider may assess changing the dispensing frequency to weekly, and document the reason (s) for changing. No doses are observed even if the patient is coming to the clinic and picking up medications weekly.

2.12. Visit schedule, measures, and laboratory samples

Research visits are the same for all participants, regardless of assigned treatment arm (Table 1). In addition to the enrollment baseline visit, 16 additional visits will take place at weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, and 168 for participants who initiate treatment. At each visit, research staff administer questionnaires, provide counseling on avoidance of HCV and HIV infection, offer information on drug treatment and syringe services programs, and other referrals as needed, such as health and social services. Urine specimens are collected at baseline and weeks 4, 8, 12, 24, 48, 72, 96, 120, 144 and 168 and tested for drugs, including amphetamine, barbiturate, benzodiazepine, buprenorphine, cocaine, THC/Cannabinoids, methadone, methamphetamine, opiate, and oxycodone (Multi-Drug Screen Dip Card 10 Panel; American Bio Medica Corp.,Kinderhook, NY), The oxycodone assay has a higher sensitivity than the opiate assay in detecting certain opioids in urine, including oxycodone (OxycContin ®), hydrocodone (Vicodin®) and hydromorphone (Dilaudid ®). At weeks 4, 8, 12, and 24 medical records are reviewed for evidence of HCV viremia, as the participant's healthcare provider may order this test to monitor the result of treatment. A blood sample (20 mL of whole blood) is collected at visit 1 (baseline visit) for archiving. Additional blood samples (20 mL whole blood for viremia testing and archiving) are collected at weeks 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, and 168.

2.13. Planned statistical analyses

The six outcome variables are: 1) SVR rates among those randomized to mDOT compared to those randomized to PN (primary outcome), 2) treatment initiation, 3) longitudinal biweekly treatment adherence rates, 4) treatment completion, 5) development of drug resistance, and 6) reinfection. First, the distributions of all variables will

Table 1
Core assessment measures.

Research visit activities	Time (minutes)	Pre-treatment			Treatment visits			Post-treatment visits		
		Pre-screening	Enrollment	Baseline	Week 4, ± 1 wk	Week 8, ± 1 wk	Week 12, ± 1 wk	Week 24, ± 2 wks	Week 36, ± 2 wks	Week 48, ± 2 wks
Visit number			0	1	2	3	4	5	6	7
TIME (in minutes)			40	70	37	22	90	70	20	65
Release of information		X	X							
Informed consent	30		X							
Randomization			X							
Instruments										
Socio-demographic survey	10		X							
Short socio-demographic survey	5							X		
Behavioral risk assessment	10			X	X		X	X	X	X
Depression (PHQ-9)	5			X			X	X		X
Anxiety (GAD-7)	4			X			X	X		X
Alcohol use (AUDIT-C)	3			X			X	X		X
Modified ASI – baseline	10			X						
Modified ASI – follow-up	5				X	X	X	X		
Substance use treatment	3			X	X	X	X	X		X
Quality of life (EQ-5D)	8			X			X	X		X
Adherence (visual analogue scale)	2				X	X	X			
Medical outcomes social support scale	5			X			X			X
Brief revised working alliance (PN arm only)	5						X			
Stigma scale	5			X						
Shame scale	2			X					X	
Health efficacy scale	3			X			X			
Satisfaction scale	1						X			
Peer support	1			X	X	X	X	X		
Labs										
HCV antibody		MC		MC						
HCV viremia		MC		MC	MC	MC	MC	MC	X	X
HCV genotype/subtype				MC	MC					
HIV test				MC						
HIV viral load*				MC	MC	MC	MC			
HIV CD4*				MC	MC	MC	MC			
AST/ALT/Platelets/ FIB-4 calculation		MC		MC	MC	MC	MC	MC		
Total bilirubin				MC						
Albumin				MC						
Prothrombin time				MC						
FibroSure/Fibroscan/Liver biopsy				MC	MC**	MC**				
Imaging study**		MC		MC						
Child-Pugh score (exclude B,C)				MC	MC	MC	MC			
Pregnancy test*				MC						
Archiving sample				X				X	X	X
HCV GenoSure NS5A/NS5B Assay*								X		
HBV panel				MC						
HAV status				MC						
Urine toxicology POC assay				X	X	X	X	X		X

(*continued on next page*)

Table 1 (*continued*)

Research visit activities	Post-treatment visits									
	Week 60, ± 2 wks	Week 72, ± 2 wks	Week 84 ± 2 wks	Week 96, ± 2 wks	Week 108, ± 2 wks	Week 120, ± 2 wks	Week 132, ± 2 wks	Week 144, ± 2 wks	Week 156, ± 2 wks	Week 168, ± 2 wks
Visit number	8	9	10	11	12	13	14	15	16	17
TIME (in minutes)	15	45	15	25	15	90	15	25	15	90
Release of information										
Informed consent										
Randomization										
Instruments										
Socio-demographic survey										
Short socio-demographic survey		X				X				X
Behavioral risk assessment	X	X	X	X	X	X	X	X	X	X
Depression (PHQ-9)						X				X
Anxiety (GAD-7)						X				X
Alcohol use (AUDIT-C)		X		X		X		X		X
Modified ASI – baseline										
Modified ASI – follow-up		X				X				X
Substance use treatment						X				X
Quality of life (EQ-5D)						X				X
Adherence (visual analogue scale)										
Medical outcomes social support scale						X				X
Brief revised working alliance (PN arm only)										
Stigma scale										
Shame scale						X				X
Health efficacy scale										
Satisfaction scale										
Peer support										
Labs										
HCV antibody										
HCV viremia	X	X	X	X	X	X	X	X	X	X
HCV genotype/subtype										
HIV test										
HIV viral load*										
HIV CD4*										
AST/ALT/Platelets/										
FIB-4 calculation										
Total bilirubin										
Albumin										
Prothrombin time										
FibroSure/Fibroscan/Liver biopsy										
Imaging study**										
Child-Pugh score (exclude B,C)										
Pregnancy test*										
Archiving sample	X	X	X	X	X	X	X	X	X	X
HCV GenoSure NS5A/NS5B Assay*										
HBV panel										
HAV status										
Urine toxicology POC assay		X		X		X		X		X

Note: MC = Medical chart; * = if applicable; ** = if available.

be examined using graphical or descriptive statistics to identify any values out of range. When identified, out of range values will be verified by checking the original record, compared and corrected if needed. Second, although each arm will equally be distributed across city, clinical site (OTP and CHC) and stage of liver disease (cirrhosis vs. no cirrhosis) by the stratified randomization design, the success of randomization will be monitored as a way of checking key assumptions by comparing the PN and mDOT groups on key variables, including demographic, behavioral, and clinical characteristics. Continuous variables will be compared between arms using the *t*-test or Mann-Whitney test, and categorical variables will be compared using chi-square or Fisher's exact test. When necessary, normal assumptions will be checked for continuous variables by applying a formal Kolmogorov-Smirnov test, and if violated, Box-Cox transformations will be considered. All statistical analyses will be conducted using SAS v9.4 or updated version (SAS Institute Inc. Cary, NC).

The Consolidated Standards of Reporting Trials (CONSORT) and ICH-9 statistical analysis guidelines suggest that, any baseline characteristics, even if significantly unbalanced between arms, should not be included in the statistical models for the outcome analysis since baseline imbalance could be due to chance rather than systematic bias in randomized studies but include as the covariates the randomization stratification variables. In the HERO study, these variables are: site/city, clinic type (OTP and CHC) and stage of liver disease (cirrhosis vs. no cirrhosis). The primary analytic sample, nonetheless, might no longer represent a randomized pool of participants since the characteristics of participants who initiated treatments may be unequal between the two models of care which may have differential effects on triggering treatment initiations due to difference in modalities of treatment initiation and delivery. Therefore, baseline characteristics could exist that are unbalanced beyond chance among participants initiating treatment between the two arms. We will declare an imbalance if a baseline characteristic is significantly different between the two arms with a stringent two-sided p-value $< .01$, considering the multiplicity of testing. As such, we will include unbalanced baseline characteristics for adjusting purposes in the statistical models in addition to the randomization stratification variables.

Specifically, to test the overall effectiveness of PN or mDOT on the binary (success vs. failure) primary outcome such as SVR, we will apply multivariable logistic regression models which will include unbalanced baseline characteristics (if any) in addition to the three randomization stratifying variables for adjusting purposes. PN or mDOT will be the predictor for each outcome. With respect to the longitudinal adherence rates, however, repeatedly measured adherence will be analyzed using 6 post-baseline time points and adherence as a continuous measure. We will apply a multivariable mixed effects linear model to test if the two arms are significantly different. This model accounts for within-subject longitudinal outcome correlation by taking the subject-level intercept as random. Multivariable mixed effects logistic regression will also be applied to test the significance of PN and mDOT on repeatedly-measured undetectable HCV viral loads throughout the intervention period. Changes in illicit drug use will be analyzed using urine toxicology data from alternating visits, counting the “person-month” as a unit of analysis, and analyzing the percentage of person-months that are positive for use of drugs including amphetamine, barbiturate, benzodiazepine, buprenorphine, cocaine, THC, methadone, methamphetamine, opiate, and oxycodone during the study period using the *t*-test or Mann-Whitney test.

Mediation analysis will be conducted to identify potential mediators between mDOT/PN effect and each of the outcomes. A mediator will be a variable whose value changes or occurs between the baseline visit and the end of the study; for example, reduced shame, extent of peer support, changes in social support, and increased self-efficacy. The potential mediating effects will be assessed by differences in mDOT or PN effect sizes depending on outcome with and without a potential mediator variable in statistical models. The significance of mediating effects will be tested following the Baron and Kenny mediation test principle [49].

To further document the statistical analysis plans including data sources, definitions of analytic samples, algorithms determining the study outcomes, and subgroup analysis strategies, we utilized a statistical analysis plan (SAP).

2.14. Power analysis for SVR

Considering the base 80% SVR rate in PN arm, a minimum of 9% difference between the two arms can be detected (i.e. 89% vs. 80%, odds ratio (OR) = 2.1) in a multivariable regression model in which confounding variables will explain 10% of variation in the predictor variable. This study posits that a > 9% difference in SVR between the PN and mDOT groups will be clinically significant based on prior studies that showed that SVR rates in treatment naïve patients were > 90%. Mixed effects logistics regression models for the undetectable HCV viral load will be able to detect an even smaller percent point difference since they will utilize repeated measures for each subject no matter how large within-subject outcome correlations are.

2.15. Reinfection, relapse, and resistance

Reinfection will be defined by post-treatment quantifiable HCV RNA with any of the following criteria: 1) viremia with different genotype/subtype; 2) date following documentation of SVR; 3) the same genotype/subtype but with phylogenetic evidence of reinfection. For the latter, next-generation sequencing of the HVR1 sequences will compare baseline and post-treatment viremia specimens with a genetic diversity threshold set at nucleotide substitutions per site > 3% [50], verified by cluster analysis. Those with post-treatment quantifiable HCV RNA > 1000 IU/mL and not classified as reinfection will be classified as relapse and resistance will be measured for baseline and post-treatment samples with genotypes 1a, 1b, and 3 (representing over 90% of the cohort) by ultra-deep sequencing of NS5A with reporting of relevant substitutions at the 10% level (Monogram Biosciences, South San Francisco, CA). The proportion of those developing resistance or reinfection will each be calculated using exact binomial methods.

For the analysis of resistance, bivariate analysis using logistic regression with continuous and dummy-coded categorical variables will be performed; factors significant in bivariate analysis will be included in a multivariable logistic regression. For the analysis of reinfection, the time to reinfection from SVR will be determined and the date of reinfection will be estimated by using the midpoint date between the date of the last undetectable HCV RNA test and the date of the first detectable HCV RNA test. The incidence of reinfection will be calculated by the number of incident infections divided by the number of person-years (py) of follow-up. Log-rank test will be applied to test difference in time to reinfection between two arms and also to identify categorical factors that are associated with reinfection. Bivariate cox proportional hazards regression models will be used to identity continuous variables and then a multivariable cox regression models will be applied primarily to test significance of the study arm in the presence of potential confounding factors. Both the adjusted and unadjusted Kaplan-Meier curves will be presented.

2.16. Qualitative interviews, methods and analysis

2.16.1. PN qualitative study

2.16.1.1. Recruitment. Between 10 and 15 patient navigators, with at least one navigator from each site, will be recruited in Year 1 to complete an in-depth interview. Data are utilized as part of a formative evaluation, to identify emerging barriers to program success and facilitate problem solving [46] [51].

2.16.1.2. Data collection. After informed consent is obtained, patient

Table 2
Data collection plan for assessing implementation outcomes.

Variables	Data collection and source	Responsible	Method of data analysis	Responsible
Acceptability of intervention				
Patient. satisfaction with treatment	1 treatment satisfaction question	Site RA	Quantitative	Site RA
Positive/negative experiences with treatment	Brief treatment experiences interview at various time points	Site RA	Structured, 'quantitated' thematic analysis w/ qual data analysis program	Bronx Implementation Team
Feasibility of intervention				
Recruitment milestones	Research database	Site staff	Quantitative	Local/New Mexico
Retention in intervention	Research database	Site staff	Quantitative	Local/New Mexico
Execution of work plans	Work plans for each arm and milestones and dates achieved	Bronx Project Director	Qualitative	Bronx Implementation Team
Intervention dose				
mDOT				
# Observed doses/# Planned observed doses	Nurse calendar/log or patient log	Frontline staff	Qualitative	Local/NM
Patient navigation				
2 in Person meetings/3 follow-up calls	Case notes or other records	Frontline staff	Qualitative assessment and quantitative tabulation	Site Staff Supervisor
Fidelity of PN intervention to be discussed with DOH PN team				
Care plan completed	Navigation care plan	Frontline staff	Qualitative, assessment, tabulation	PN records
Initial medical evaluation completed	Case notes	Frontline staff	Qualitative, assessment, tabulation	PN records
Referrals made	Case notes	Frontline staff	Qualitative, assessment, tabulation	PN records
Referrals followed up	Case notes	Frontline staff	Qualitative, assessment, tabulation	PN records
Education sessions 1 and 2 provided	Attendance records/groups, case notes/ ind. # Minutes	Frontline staff	Qualitative, assessment, tabulation	PN records

Consent	Data collection instruments
Site leader oral consent	• Site leader interview • Site leader guide post implementation
Staff oral consent	• Brief staff interview • Frontline staff interview post implementation
Patient oral consent	• Brief patient experience interview • Patient treatment experiences and barriers/facilitators to treatment
Request waiver of consent-anonymous on worksite culture	• Grumbach questionnaire
Regular study consent form-to be embedded in 12-week follow-up interview	• Working alliance questionnaire

navigators complete a 30-min semi-structured interview with a trained qualitative expert focusing on their experience and perception of the intervention, to capture the perspectives of these front-line patient navigators on the barriers to successful patient outcomes (Table 2).

2.16.1.3. Analysis. Interviews will be recorded and transcribed. Data are analyzed using Miller and Crabtree's "Editing" approach [47,52]. A preliminary coding scheme will be created and revised in iterative fashion as it was applied to new subsets of data. The complete data set will be coded in NVivo (QSR International, Pty Ltd., 2017), a qualitative data analysis program that facilitates the rapid organization and retrieval of thematically related data [53–56]. Themes related to successes and failures, and sources of stress and satisfaction will be summarized. Data summaries will be presented to the NSAB to discuss implications, identify emerging problems, and find solutions.

2.16.2. Patient qualitative study

The focus of the patient study, conducted in years 2–6, is to understand barriers to successful outcomes along the pathway to care, including lack of treatment initiation, poor adherence (< 80%), failure to achieve SVR, development of drug resistance, and HCV reinfection. The patient study incorporates a comparative design, whereby structured comparisons are made between successful and non-successful patients at each stage along the care cascade with the goal of identifying barriers to successful treatment.

2.16.2.1. Recruitment. Approximately 10 participants who successfully initiated treatment and 10 who did not initiate treatment will be recruited and interviewed, with the goal of including at least one patient in each category by site. Similarly, participants who adhered/did not adhere, achieved SVR/did not achieve SVR; and those who become reinfected/remained HCV-free will be recruited and interviewed. In keeping with standard qualitative methodological procedures, sample sizes are approximate, and sampling will continue until theoretical saturation is achieved.

2.16.2.2. Data collection. Participants will be telephone interviewed by a trained interviewer, using an interview guide focused on barriers and facilitators to successful treatment, perceptions of the intervention, perceived need for treatment, relationships with research staff, and treatment experiences. The guide includes questions on contextual barriers to successful participation such as economic, social, and psychological stressors, as well as facilitators such as social support and other resources. The interviews are recorded and transcribed for analysis.

2.16.2.3. Qualitative data analysis. Data analysis will proceed in two steps. The first step entails the standard data analysis approach described above. In the second step, the analysis team will make structured comparisons across successful and unsuccessful patients, searching for patterns in the data that reveal core differences across groups and provide insight into why some patients are able to succeed with treatment and some are not. Data from these comparative analyses will be summarized and presented to the Stakeholder team, with the

goal of improving the capacity of the intervention team to provide patient-centered care and better meet patient needs. Data collected in later years of the project will be used as part of a summative evaluation, to understand the successes and failures of the intervention with the goal of improving the effectiveness of future interventions.

3. Discussion

This study represents the first randomized pragmatic trial comparing the effectiveness of mDOT compared to PN in treating HCV in PWID who are actively injecting. Studies of HCV treatment outcomes in PWID have included various subpopulations, including those who are no longer injecting drugs and those who are enrolled in OTPs. There are, to date, no published prospective studies which restrict the PWID population to those actively injecting any substance within 90 days of enrollment.

The HERO study will provide valuable information on optimal models of care to promote HCV treatment initiation, adherence, treatment completion and SVR among PWID. We will also examine rates of resistance development and reinfection up to 3 years. Understanding these factors is crucial to addressing the HCV epidemic in this high-risk population. Reviews and guidelines emphasize that further research on the effects of different models of care is needed to provide recommendations on the most effective way to provide curative HCV therapy to PWID. The HERO study addresses this critical need [6–8,14]. We expect that the results of this study will advance knowledge regarding the effectiveness of both mDOT and PN for HCV treatment support for PWID and inform modifications and variations to both models of care.

The use of electronic blister pack technology to monitor adherence is innovative. In the interferon (IFN) era, strict adherence to combination IFN and ribavirin (RBV) was necessary to optimize SVR rates. In the DAA era, adherence remains a critical issue for achievement of SVR and reducing risk of developing resistance [57], but as there are currently limited data describing associations between DAA adherence and virologic outcomes, optimal adherence to DAA regimens is not known. Accurate measurement of adherence will be an indispensable element to understand the direct effect of nonadherence on treatment failure. Previous randomized trials that focused on DOT for pegylated-IFN and RBV utilized diaries and pill counts to measure adherence [58–60]. Use of electronic blister packs in HERO will build on this literature by measuring adherence using electronic monitors that have been shown to better predict virologic outcomes in HIV-infected populations [7,20,61].

The HERO study has several strengths. First, it is focuses on people who are actively injecting substances as defined by injection drug use within 90 days prior to enrollment. Prior studies have not used specific criteria and often have mixed populations of people actively injecting drugs and those who injected in the past. It is necessary to treat people who are actively injecting in order to interrupt transmission and reduce incidence. Secondly, HCV treatment in this study is delivered in community-based clinical settings where PWID seek care. Community-based models of care are consistent with the current recommendations to expand treatment to primary care settings. Third, HERO sites have significant geographic and state policy diversity, including variable Medicaid restrictions of DAAs for PWID. Therefore, our results represent the implementation of the interventions in these diverse settings and as such provide valuable insights on real-world effectiveness given these heterogeneities. Fourth, we include PWID both maintained and not maintained on opioid agonist treatment. Fifth, our study is unique in that the eight sites provide a robust sample size for a study of PWID which will allow important subgroup analyses for heterogeneity. For example, additional analyses will be conducted to evaluate whether the mDOT and PN effects varies by subgroups stratified by the following characteristics: OTP vs. CHC; men vs. women; African-American/Latino vs. Caucasian; unstable housing vs. stably housed; illicit drug use during treatment vs. no illicit drug use during treatment; HIV/HCV co-infected vs. HCV mono-infected; cirrhotic vs. non-cirrhotic; severe to moderate anxiety symptoms vs. mild to minimal; and, severe to moderate depression symptoms vs. mild to minimal. Sixth, the use of a pan-genotypic medication (sofosbuvir/velpatasvir) allows inclusion of DAA-naïve PWID irrespective of their genotype. Seventh, we include several important patient-reported outcomes such as shame and stigma that have not been included in other HCV treatment studies in PWID. Finally, this is the largest study to measure rates of reinfection in active PWID who successfully complete HCV treatment. Our results will likely inform modeling studies regarding optimal HCV elimination strategies and should have important policy implications.

The HERO study does have some limitations. Most of our study sites are located in urban areas although two sites also serve rural participants seeking care in the adjoining urban areas (e.g. Albuquerque, New Mexico, and Morgantown, West Virginia); PN and mDOT models of care may have different effects in nonurban settings. Second, our sites serve PWID who predominantly are of low socioeconomic status. It is unclear if these same interventions will be effective or preferred by PWID of higher socioeconomic status. Finally, the study is conducted in 23 different clinical settings in eight cities which may lead to variability in fidelity; as we are measuring fidelity (Table 2) to the mDOT and PN interventions we will attempt to account for these differences in the analyses.

The HERO study is the largest study to date investigating the effectiveness of different models of curative HCV treatment in people who are injecting drugs and will likely have important policy implications as we move towards the WHO goal of HCV elimination by 2030.

HERO study group

Clemson/Prisma Health: Alain H. Litwin, Moonseong Heo, and Irene Pericot-Valverde. Harvard Medical School: Arthur Y. Kim, William Schmitt, Virginia Lijewski, and Jillian Roche. University of Rhode Island: Lynn E. Taylor, Karen Tashima, Sophie Sprecht-Walsh, Melissa Hordes, and Ellie MacGregor. Montefiore Medical Center: John Jost, Brianna Norton, Linda Agyemang, Julia Arnsten, Diane M. McKee, Alison Karasz, and Paul Meissner. Johns Hopkins University: Shruti Mehta, Courtney Borsuk, and Oluwaseun Falade-Nwulia. West Virginia University: Judith Feinberg and Samuel Wilkinson. University of New Mexico: Kimberly Page, Cristina Murray-Krezan, Katherine Wagner, Vanessa Jacobsohn, and Karla Thornton. University of California San Francisco: Paula Lum, Ellen S. Stein, and Annie Luetkemeyer. University of Washington: Judith I. Tsui, Kendra L. Blalock. Stakeholders: John Ward (CDC), Alice Asher (CDC), Nirah Johnson (NYC Health Department), Andrew Reynolds (Project INFORM).

Declaration of competing interest

Authors: AHL is a consultant/advisor and has received research grants from AbbVie, Gilead Sciences, and Merck Pharmaceuticals. JJ, KW, MH, AK, SM, AK, LT, PL, and IPV have nothing to declare. JF is a consultant/advisor and has received research grants from Gilead. JT is the recipient of a Small Business Innovation Research (SBIR) grant from NIH/NIDA (R44DA044053; PI: Seiguer/Tsui) in partnership with a health technology company (emocha) to research the feasibility of using smartphone app to improve adherence to office-based buprenorphine treatment. KP has received research funding from Gilead Sciences for research unrelated to this project.

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each of the 9 sites, PIs from the CDC and the NYC DOH, statisticians and key staff (such as project directors and patient representatives), and key stakeholders. HERO study sites include: Prisma Health and Clemson University, Albert Einstein College of Medicine/Montefiore Medical Center, University of Rhode Island, Johns Hopkins Bloomberg School of Public Health, Massachusetts General Hospital, University of California, San Francisco, University of New Mexico, University of Washington, and West Virginia University.

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