1

2    Patient-Centered HCV Care via Telemedicine for Individuals on Medication for Opioid Use Disorder:

3    **T**elemedicine for **E**valuation, **A**dherence, and **M**edication for Hepatitis **C** (TEAM-C)

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11   Supplement abbreviations: PWOUD, persons with opioid use disorder; HCV, hepatitis C virus; OTP, opioid treatment
12   program; MOUD, medications for opioid use disorder; DAA, direct acting antiviral; PAC, patient advisory committee;
13   OUD, opioid use disorder; OASAS, Office of Addiction Services and Supports; UB, University at Buffalo; IRB, institutional
14   review board; CARF, Commission on Accreditation of Rehabilitation Facilities; SVR, sustained virological response; DAST-
15   10, Drug Abuse Screen Test; PSQ, Patient Satisfaction Questionnaire; MMS, Modified Mini Screen; NIDA, National
16   Institute on Drug Abuse; GLMM, Generalized Linear Mixed Models; ICC, intraclass correlation coefficient.

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**SUPPLEMENTARY MATERIAL**

**APPENDIX A**

25

26    In Appendix A, additional information is provided regarding the "Methods" and the "Statistical Analyses" sections of the
27    main paper. In particular, we describe below the study population, the study sites, the randomization scheme
28    implemented, the choice of the sample size, as well as the questionnaires/instruments used. Moreover, regarding the
29    "Statistical Analyses" and the plans made for both the primary and the secondary aims, we describe the data collection
30    processes, how we handled missing data, we discuss the appropriate analysis to be used for the heterogeneity of
31    treatment effects, the exploratory aim of analysis of participant re-infection after HCV elimination, and the analysis of
32    patient satisfaction along with qualitative analytical methods.

33

34    **A.1.      METHODS**
35
36    A.1.1    Study setting
37
38    A.1.1.1 Description of the population: Persons with opioid use disorder (PWOUD) are often considered difficult-to-
39    engage in medical care as the population suffers from a variety of conditions and social determinants of health barriers,
40    such as unstable housing, food insecurity and financial difficulties, which can complicate their pursuit of hepatitis C virus
41    (HCV) treatment. Furthermore, PWOUDs often harbor feelings of mistrust and discomfort in conventional healthcare
42    settings [1]. In contrast, our study sites provide a supportive multi-disciplinary environment that includes clinicians,
43    nurses, social workers, counselors, and mental health professionals designed to enable PWOUD to address health and
44    social issues. Study participants frequently report that they consider the opioid treatment program (OTP) a trusting
45    "community" with reduced stigma and increased comfort in which they routinely form their own peer-based social
46    networks (e.g., the peer pipeline) [2-4] as well as developing trusting rapport with the clinic staff. PWOUD also place a
47    premium on medications for opioid use disorder (MOUD) as it is considered by many an essential lifeline to health [5].
48
49    OTP staff are invaluable in their support of the study. Counselors facilitate PWOUD participation, engagement, and
50    contact while nurses, who are largely responsible for direct acting antiviral (DAA) and MOUD dispensing, also emphasize
51    DAA adherence. OTP clinicians are critical for early DAA side effect management, and they reassure and reinforce DAA
52    adherence in cases of disruption. We were able to introduce the study through the sites' patient advisory committees
53    (PACs). The PACs play an extremely important role in participant identification and encouragement. The sites' PACs also
54    offer an opportunity to promote PWOUD education about HCV and DAAs, which had recently been introduced into
55    clinical practice at the time when the study was initiated.  Study staff educated OTP staff about HCV pathogenesis and
56    therapeutic changes that occurred as a result of DAAs. Thus, a reciprocal relationship has been established whereby the
57    OTP benefits the research project by providing opportunities for routine participant interaction and linkage strategies in
58    the case of participant disappearance, as well as facilitating study data collection. The study benefits the OTP by
59    facilitating the integration of opioid use disorder (OUD) and HCV management, thereby fostering a more comprehensive
60    level of healthcare delivery and improvement in liver health outcomes.

61    PWOUD can have multiple competing priorities and rapidly changing life circumstances that may thwart pursuit of HCV
62    treatment. Therefore, we attempt to enroll participants from this population, and we collect sufficient data to enable us
63    to characterize the population's stability. To accurately describe relative stability of the population and to assess MOUD
64    adherence, we collect the following variables at each clinic visit: 1) methadone medication name and strength, 2)
65    methadone dose, 3) frequency of methadone administration, 4) number of months study participant is enrolled in
66    methadone treatment, 5) if the participant missed any methadone doses in the past two weeks, 6) the number of
67    missed doses, and 7) the reason for missed methadone doses. As a relatively high percentage of PWOUD who initiate

68 MOUD discontinue within the first three months [5], therefore we require at least six months on methadone for study
69 inclusion.
70
71 A.1.1.2 <u>Study sites and regulatory approvals</u>: The study is being conducted at 12 OTPs. Five sites are all located in
72 Brooklyn. One site is located in Manhattan. Two sites are located in Central New York, one in Newberg and one in
73 Syracuse. Four sites are located in Western New York, two in Rochester and two in Buffalo. Of the study sites, four are
74 affiliated with academic institutions, four are affiliated with healthcare systems, and four are community sites. New York
75 State Office of Addiction Services and Supports (OASAS) procedural oversight and mandates do not vary whether an OTP
76 is affiliated with an academic institution, healthcare system, or community organization. Furthermore, each site has its
77 own administrator who supervises and is responsible for day-to-day clinic operations.
78
79 Regulatory approval was initially obtained from the coordinating site's (University at Buffalo [UB]) institutional review
80 board (IRB) and subsequently from the boards at each of the major subsites. We also had to obtain regulatory approval
81 from OASAS to permit us to conduct telemedicine encounters for HCV, a medical condition, at OTPs whose primary
82 objective is MOUD. Furthermore, we had to ensure that HCV management procedures were consistent with the
83 credentialing authority regulating each site, either the Joint Commission in the case of programs belonging to hospital
84 systems or the Commission on Accreditation of Rehabilitation Facilities (CARF) in the case of community sites.
85

86 A.1.2.   Randomization

87 Randomization increases internal study validity and the benefits of it apply also to stepped-wedge trials [6, 7]. In
88 particular, in the context of a stepped-wedge trial, the implementation of randomization allows the effect of time to be
89 estimated from the data. Bias that may arise from secular (i.e., temporal) trends can be controlled through appropriate
90 specification of these trends in the models used to analyze the data.
91
92 In our context, arm assignment is at the cluster (i.e., clinic) level. The order in which the telemedicine intervention is
93 received is randomized, and the data are collected from clusters over time. Key aspects of the allocation strategy are the
94 total number of clusters, the number of clusters per group, and the length of time between successive crossover points,
95 that is, the step length.
96
97 We use covariate-constrained randomization [8-10]. This procedure reduces the set of all possible randomizations to a
98 subset in which differences between the baseline covariates in the study arms have been minimized. Criteria for
99 "reasonable" baseline balance across arms are chosen and only randomizations that satisfy these criteria are
100 "acceptable". The final randomization order is obtained by drawing at random one of the "acceptable" randomizations.
101 Early on in the trial, two of the participating clinics had to be colocated on the same floor of the same building. The
102 study investigators were concerned that the aforementioned situation has the potential to introduce bias in treatment
103 uptake in favor of the intervention. This concern prompted the first specification that defines an "acceptable"
104 randomization order, that is, that the two clinics must enter the intervention arm together. The second specification is
105 based on imposing tolerance limits on covariates the investigators thought might act as potential confounders. These
106 covariates are surrogate biologic covariates of sustained virological response (SVR) and some demographic covariates
107 that have the potential to introduce confounding. Surrogate biologic covariates are age (because it acts as a surrogate
108 for infection duration), gender and race, while the demographic variable, ethnicity, is used because of substantial
109 variation in the composition of different clinics. We note here that substantial variation in terms of gender and race was
110 observed among the different clinics. Clinic-based covariates were considered and include physician and nurse staffing
111 ratios (because of their importance as factors in participant adherence and retention). However, because these were
112 similar between clinics and OASAS mandated, they were not included in the randomization. All categorical covariates
113 were assigned a 0.3 (or $c_j = .3$) tolerance margin, while the single continuous covariate, age, was assigned 0.2 ($c_j = .2$)
114 tolerance margin. That is, covariates that are dichotomous, such as gender (male/female), race (White/African-American
115 and other) and ethnicity (Hispanic/Non-Hispanic) were balanced within $\pm$ 30%, while the mean age for each arm is within
116 $\pm$ 20% of each other. The specification criterion is given as

117

$$\frac{1}{(1+c_j)} < \frac{\sum_{i=1}^{12}[36-(t_i-1)]x_{ij}}{\sum_{i=1}^{12}(t_i-1)x_{ij}} < 1 + c_j,$$

119

120 where $x_{ij}$ is the $j$th covariate for the $i$th clinic, $t_i \in \{10,19,28\}$ is the set of entry months (step length is 9 months). This
121 means that the sum of the covariate values weighted by the number of months in the intervention status, that is
122 telemedicine, must be within $c_j \times 100\%$ of that of the usual care (or control) arm. This randomization procedure has
123 been used successfully in a number of trials (see, for example, [10]). The computer program was communicated to us by
124 Dr. Moulton (personal communication to M. Markatou).

125

126 In total, there are 34,650 possible allocations of 3 groups containing 4 clinics per group. The number of "acceptable"
127 allocations, that is, those that obey the set of the aforementioned restrictions are 2,442. The final allocation is chosen as
128 follows: we randomly select 10 allocations out of 2,442 and then select randomly from these 10, the implemented
129 allocation.

130

131 The final randomization order was kept confidential. Sites that were crossing to the intervention arm were notified after
132 completion of enrollment for the specific period and 30 days before the occurrence of the crossover, while the rest of
133 the randomization order was kept confidential from all other sites. Thus, sites that continued the usual care arm were
134 not informed about which sites implemented the intervention or when it would be implemented at their sites. Bias was
135 minimized since neither the sites nor the participants were aware of when telemedicine-based evaluations would open
136 at their sites. Participants who were motivated to be treated for HCV were enrolled first and there was no warehousing
137 of participants. Sites adhered to the randomly determined roll-out of the intervention. Furthermore, to avoid
138 contamination between the two arms, we maintained lists of individuals participating in the usual care and telemedicine
139 arms to avoid usual care participants entering into the telemedicine arm.

140

141 A.1.3.   Research implementation strategies
142 In order to conduct a rigorous clinical trial at study sites that generally had limited research experience, we provided
143 education on research conduct and developed workflows to support research. Study and site staff are integral to the
144 study conduct. Each study site has an onsite case manager who facilitates all study-related activities including participant
145 recruitment, telemedicine encounters, data collection, and participant engagement. We also established a study-wide
146 PAC with two representatives from each of the 12 study sites. The study PAC members were very helpful in publicizing
147 the study, in identifying potential study participants, in addressing study-related issues, and in ultimately disseminating
148 study results. The PAC meets quarterly via virtual technology.

149

150 In terms of education, we initiated the process with introductory meetings with each site. During the site selection and
151 study implementation phase, we conducted an onsite readiness assessment to identify issues, infrastructure, and
152 personnel critical to research study participation. We held introductory meetings at each site to discuss implementation
153 of study procedures. During the introductory meetings, we also inquired and collected information about each sites'
154 practices (i.e., number of providers, practice culture, and referral mechanisms) for referral to an HCV specialist. These
155 meetings also enabled us to establish a framework for interactions between site OTP staff and study staff. In many
156 cases, study staff were able to leverage existing relationships between counselors and study participants ("trust by
157 proxy"). In fact, counselors frequently served as the first point of contact between potential study participants and study
158 staff. Counselors routinely referred potential study participants and were extremely helpful in locating participants who
159 fell out of contact or serving as liaisons in the case that participants were hesitant or delayed study procedures, such as
160 in the case of venipuncture. Nursing staff was responsible for dispensing HCV medications simultaneously with
161 methadone as well as for preparing appropriate HCV medication quantities (*i.e.,* take home doses) for participant self-
162 administration during periods of absence from the OTP. For ease of dispensing for variable periods of time for self-
163 administration, the specialty pharmacy provided HCV medications in single doses. Nurses also encouraged and, in many
164 cases, documented HCV medication adherence. They served as a first contact point in case of substantial nonadherence
165 or adverse effect issues. In these situations, nurses would notify the study case manager or onsite clinician, as

166 appropriate. In rare instances, such as severe mental health issues or perceived side effects by study participants, nurses
167 would initially address participant's nonadherence with the study case manager or onsite clinician. The onsite clinician
168 would then address the issues directly with the participant potentially with the involvement of the telemedicine
169 clinician.
170
171 The OTP clinician was extremely helpful during telemedicine encounters. The onsite clinician facilitated the treatment by
172 initially serving as a recognized member of the treatment team. We found that participants' relationships with onsite
173 clinicians assisted in establishing rapport with the telemedicine provider. During the initial telemedicine encounter,
174 participants were explained the credentials of the telemedicine provider, and they were educated about principles of
175 telemedicine. The encounter also addressed potential concerns, including privacy and confidentiality during the visits
176 and privacy of protected health information. The participants had a complete medical history and physical examination
177 that were performed jointly between the telemedicine provider and the onsite clinician. The onsite clinician was
178 available in the case of severe side effects that required immediate attention and if participants had adherence issues,
179 which might occur in the case of severe side effects, or if participants had mental health issues. Particularly in the case of
180 severe mental health issues, study participants transfer of trust to the telemedicine provider was critical for successful
181 telemedicine encounters, and the telemedicine provider was considered an extension of the OTP clinical staff [11].
182
183 A.1.4. Engagement principles
184 In order to conduct a rigorous clinical trial, we developed the CREATE framework (CREATE-**C**ulture, **R**espect, **E**ndorse,
185 **A**dvantage, **T**rust, **E**ngagement) to guide PWOUD involvement in research. The **C**ulture within the OTP should support
186 research. The researchers and intervention should demonstrate **R**espect for study participants and OTP staff, which
187 typically leads to their **E**ndorsement of the intervention. Once exposed to the intervention, in this case telemedicine
188 treatment of HCV, PWOUD appreciate its **A**dvantages over offsite referral and over time develop **T**rust in the
189 intervention. Ongoing **E**ngagement activities (e.g., meals, education, appreciation events) are important to sustain
190 participation and retention over time. We found that holding twice yearly study updates and appreciation events, such
191 as breakfast or lunch delivered to staff that also included PAC members, were important to maintain engagement. The
192 CREATE framework highlights important attributes that we have learned promote PWOUD engagement and retention in
193 research.
194
195 A.1.5  Instruments (Questionnaires)
196 We collected information through a variety of different questionnaires to enable us to address the secondary study
197 objectives related to patient-centeredness, specifically to compare patient satisfaction with healthcare delivery between
198 the two arms and evaluation of the satisfaction with HCV treatment via telemedicine.  These instruments also enabled
199 us to ascertain important information about the study population.
200         Table 2 briefly describes each questionnaire and illustrates the timepoints when each instrument is
201 administered by study arm. Of note, all instruments are administered only once with the exception of the Drug Abuse
202 Screen Test (DAST-10) and the HCV Patient Satisfaction Questionnaire (PSQ), which are administered twice at two
203 separate visits. The Modified Mini Screen (MMS), National Institute on Drug Abuse (NIDA) Quick Screen, DAST-10 and
204 the HCV PSQ have all been validated previously.
205         a.        Demographic Survey-The goal of the demographic survey is to obtain baseline demographic information
206 about the study participants including primary language, anthropomorphic measurements, social situation, comorbid
207 medical conditions, social support, and potential HCV risk factors.
208         b.        Sociodemographic Survey-This instrument queries about participant demographics, mental health and
209 substance use issues, living situation, household income, educational level obtained, English language proficiency,
210 availability of medical insurance, and incarceration.
211         c.        MMS-A generic screening measure for mood, anxiety, and psychotic spectrum disorders. Sectional and
212 overall scores are calculated based upon the percentage of yes responses. The questionnaire has been validated by
213 Alexander et al [12].

214       d.       NIDA Quick Screen-The NIDA Quick Screen is designed to screen for substance use including the use of
215 drugs (mood-altering, illegal, or prescription for nonmedical reasons), alcohol, or tobacco products within the past year
216 as well as how often these substances have been used [13]. It has been validated by NIDA.

217       e.       DAST-10 is a self-reported instrument for population screening, clinical case finding, and treatment
218 evaluation research. The test yields a quantitative index of the degree of drug abuse consequences [14, 15]. The DAST-
219 10 has been validated by NIDA. The DAST-10 enquires about drug use in the preceding 12 months. Since an average of 7
220 months elapsed between Visit 1 and Visit 8, the initial DAST-10 administration would have inquired about drug use in
221 the 12 months preceding study participation and the second, 5 months prior to study participation.

222       f.       HCV PSQ-This instrument is based upon the PSQ-18 [16] that was derived from the extended PSQ-III
223 Survey that contained 50 items. The instrument captures global satisfaction with medical care, technical quality,
224 interpersonal manner, communications, financial aspects of care, time spent with the physician, and accessibility of care.
225 The questionnaire was modified slightly to inquire about quality of care for HCV as opposed to general medical care.
226

227       **Table A.1:** List of instruments with the corresponding visit of their assessment stratified by study arm

| Instrument Name | Visit(s) at which the instrument is administered by arm | |
| | Referral | Telemedicine |
| --- | --- | --- |
| SAMHSA Educational Brochure | Screening | Screening |
| Demographics | Visit 1 | Visit 1 |
| Sociodemographics | Visit 1 | Visit 1 |
| Modified Mini Screen | Visit 1 | Visit 1 |
| NIDA Quick Screen | Visit 1 | Visit 1 |
| DAST-10 | Visits 1 & 7 | Visits 1 & 8 |
| HCV Patient Satisfaction Questionnaire | Visits 2 & 7 | Visits 2 & 8 |

228       Abbreviations: SAMHSA, Substance Abuse Mental Health Services Administration; NIDA, National Institute on
229       Drug Abuse; DAST-10, Drug Abuse Screen Test; HCV, hepatitis C virus.

230 **A.2.     STATISTICAL ANALYSES**
231

232 The primary outcome of interest is the SVR rate in the two arms, and primary interest is centered on the comparison of
233 the SVR rates between usual care and telemedicine. Other outcomes of interest include: 1) treatment initiation rates as
234 measured by the proportion of individuals who take an initial medication dose; 2) treatment completion rates; 3) HCV
235 adherence as measured by methadone adherence, which in turn is measured by the number of unexplained missed
236 doses in the two weeks preceding any study associated visit; 4) patient satisfaction with the telemedicine-based HCV
237 care scores using the adapted PSQ [16, 17]; and 5) reinfection rates.
238

239 Treatment initiation and completion rates will be analyzed graphically, presenting the associated rates in the two arms
240 per period and per cluster per period. Similarly, the HCV adherence rates for the two arms will be reported. Details on
241 the analysis of patient satisfaction scores are reported in Section A.2.2.2, which also reports on the analysis of
242 reinfections.
243

244 We will follow the CONSORT statement for reporting of stepped wedge trials [18].
245

246 A.2.1   Analysis Plan for Primary Aims
247

248 A.2.1.1 Data Collection: Per OASAS regulations, HCV antibody levels are assessed on admission to the OTP and on an
249 annual basis. Thus, we obtained a list of potentially eligible participants who were then approached regarding potential
250 study entry. If HCV seropositive individuals agreed to study participation, they were scheduled for a screening visit
251 where the laboratory parameters mentioned in Table A.2 were obtained. Those individuals who have detectable serum
252 HCV RNA were enrolled in the study and had their levels of fibrosis and inflammation assessed at Visit 1.

253

**Table A.2:** Laboratory parameters collected at Screening Visit and Visit 1

| Screening visit | Lab test | Reason |
|---|---|---|
| | HCV antibody | Assess exposure to HCV |
| | HCV RNA | Assess active HCV infection |
| | HCV genotype | Assess type of hepatitis C |
| | CBC | Assess hemoglobin concentration |
| | CMP | Assess metabolic, renal, hepatic parameters |
| | INR | Assess coagulation parameters |
| | Toxicology screen | Assess use of illicit substances |
| | HIV antibody | Assess exposure to HIV |
| | HBV surface antigen | Assess exposure to HBV |
| | HBV surface antibody | Assess immunity to HBV |
| Visit 1 | FibroSure® | Assess liver fibrosis and inflammation levels |
| | HIV RNA | Assess active HIV infection |
| | CD4 cell count | Assess immune system status in HIV infection |

Abbreviations: CBC, complete blood count; CMP, complete metabolic panel; HCV, hepatitis C virus; INR, international normalized ratio; HBV, hepatitis B virus; HIV, human immunodeficiency virus; RNA, ribonucleic acid

A.2.1.2 <u>Missing data</u>: Missing data can occur in any study design and with any data source. In clinical trials, missing data often arise when participants drop out of the study before its conclusion [19]. Li et al, (2014) indicate that the single best approach to deal with missing values is to prospectively prevent their occurrence [20]. To this end, the study personnel attempted to minimize the amounts of missing values by following closely the study participants. The case managers were provided with a list of strategies to avoid missing values, and issues surrounding missing data were reviewed weekly during conference calls.

Specifically, the following strategies are implemented with the aim of limiting the occurrence of missing data. Adherence to the treatment schedule is monitored very closely by the case managers at each site. At a higher level, the Biostatistics and Data Management Team monitors the trial weekly. The study participants are informed at the consent stage of the importance of completing all surveys, and case managers facilitate completion by administering the surveys onsite. During the COVID-19 restrictions and because recruitment had been completed, despite an increased likelihood of the occurrence of missing data, the impact on the study was minimal. Additional strategies we have implemented include frequent reminders to study participants for study visits, education of participants of the importance of continuous engagement, keeping participant contact information current, providing monetary incentives to participants, and collecting information on participants at risk of dropout.

To deal with statistical challenges around missing data, we collect detailed information on the reasons for missingness when missing data occur. Whenever a participant discontinues all or some type of study participation, we document the following: 1) the reason for discontinuation, 2) type(s) of participation that the discontinuation involves, and 3) who decided on the discontinuation of the participant from the study. For example, in the case of ongoing non-adherence with OTP attendance requirements or prolonged absence, such as in the case of incarceration, the OTP may "administratively discontinue" an individual. If a study participant is discontinued from the OTP, their study participation ceases. Therefore, opportunities for follow up blood draws and obtaining study-related information were not possible.

If missing data are encountered, the following steps are taken. 1) A report is filed documenting the occurrence of missing data, potential resolution, and the expected resolution deadline. 2) The case manager investigates whether it is

possible to retrieve the data. If not, auxiliary information is collected that presents the reasons for missing data. Each site is requested to report the percentage of missing data for each participant on a weekly basis.

The above strategies severely limit the amount of missing data present. If missing data are present, the adjudication of the missing data mechanism is guided by the reasons that explain why data are missing. Use of valid statistical methods, such as multiple imputation, that properly reflect multiple sources of uncertainty will be employed if necessary, in the analysis of data, as well as reporting the percentage of missingness to allow readers to assess the validity of the findings [21].

A.2.2    Analysis Plan for Secondary Aims

A.2.2.1 Heterogeneity of Treatment Effects: Analysis of heterogeneity of the intervention effect, that is, estimation of the intervention effects in subgroups, is challenging (see [22]). Subgroups of interest have been defined "a priori", at the request of the sponsor, by the following variables: 1) comorbid medical conditions (specifically depression), 2) fibrosis stage (binary with one level including F3 and F3-F4 patients versus all other stages), 3) residence type (specifically urban/rural classification). The goal is to identify whether these factors influence the decision to initiate and to continue treatment for HCV in the two study modalities.

The percentage of PWOUD with comorbid medical conditions ranges from 20% to 85% based upon findings in the literature [22, 23].  Depression and anxiety disorders, which have been shown to have a prevalence varying from 24.5% to greater than 50%, was included as a specific diagnosis among those with comorbid mental health conditions [22-24]. Using this range and given the fact that each arm has a total sample size of 312 participants, sufficient sample size allocation of the sample per arm exists when the sample is stratified by the comorbid conditions variable to allow exploratory analyses and to generate hypotheses for further study.

The stage of fibrosis remains an important factor to evaluate as a determinant of successful viral eradication in real world settings. Based upon data from our pilot study [25], the percentage of participants with advanced fibrosis (F3 and F3-F4) as assessed by FibroSure® is 16% and the percentage of participants with cirrhosis (F4) is 12%. Correspondingly, we would estimate that 28% of the participants in each study arm would have advanced fibrosis or cirrhosis to permit evaluation of the influence of this variable on HCV treatment and virologic outcomes. We will also evaluate the percentage of study participants who reside in urban or rural areas, and the influence of this variable on HCV treatment participation.

Univariate subgroup analyses will be carried out by incorporating a treatment by factor interaction in all relevant models and adjusting for multiplicity of testing. The PWOUD population has also been substantially affected by opioid-related deaths. The main end point of the trial, measured by SVR, is a nonterminal event, yet patients may experience a terminal event, such as death, before they experience SVR. An approach to treating terminal events, such as death, is to account for it as a competing outcome that is considered simultaneously with SVR. A competing risk analysis using cumulative incidence functions to estimate the incidence of terminal events will be used, if appropriate [26, 27]. As secondary analyses are mostly exploratory in nature, we will follow Wang et al, (2007) in interpreting and reporting the results [28].

A.2.2.2 Analysis of Patient Satisfaction: Analysis of survey data will be model based. Generalized Linear Mixed Models (GLMM) will be used to account for the time effect of the HCV PSQ that is administered at two timepoints, incorporating adjustments for the clustering effect and the study arm. We will model the survey response rate as a function of demographic and other relevant covariates, as necessary.

A.2.2.3 Other Secondary Aims: Additional analyses, such as per period or per cluster descriptions, will be performed as necessary. One proposed analysis, in order to understand the stability of the PWOUD population, will be the analysis of variables collected on methadone adherence and retention (See Section A.1.1.1). These will include the characterization of longitudinal profiles of patients to obtain an illustration of adherence in each study arm. For these analyses,

continuous variables will be summarized by means/medians and discrete type variables will be summarized by percentages.

A.2.2.4 <u>Analysis of Reinfection Study</u>: An exploratory aim of the trial is the follow up of study participants for up to 24 months post-treatment cessation to evaluate for HCV reinfection. We will summarize the reinfection rates observed between the two arms of the study.  The method of analysis will depend upon the number of cases of reinfection.

A.2.2.5 <u>Qualitative methods</u>: As part of the study, we seek to understand the impact of the case managers' perceptions and obstacles of conducting research with the PWOUD population [11].  In a separate manuscript, to understand the implementation process, we will be investigating clinical and administrative staffs' experiences toward integrated clinical care via onsite telemedicine for HCV. We will utilize hermeneutic phenomenology, a qualitative approach to interpreting texts to study a phenomenon. In our initial work, we requested texts of stories and held a focus group of case managers facilitating HCV care in PWOUD. The case managers' experiences provide unique perspectives as they are the primary conduits between the participants, clinicians, and the OTP staff. We are also interviewing study participants to understand their reactions more fully to integrated HCV and OUD treatment. We will utilize hermeneutic phenomenology to identify common themes that will be combined using a mixed methods approach with quantitative data collected via the PSQ [29].

A.2.3    <u>Exploratory Analysis</u>

Distribution of all variables will be examined using graphical methods and descriptive statistics. Continuous variables will be presented by their means and standard deviations or medians and associated interquartile ranges. Categorical variables will be presented by the associated counts and percentages. Distributional assumptions will be checked via boxplots, qq-plots or other appropriate graphical techniques, and outliers will be identified via the aforementioned graphical analysis. If normality is violated, Box-Cox transformations will be considered as appropriate. All statistical analyses will be conducted using SAS (SAS Institute, Cary, NC) and/or R . The estimated intraclass correlation coefficient (ICC) will also be reported.

In addition to demographic description of the population in terms of characteristics such as age, gender, race, and ethnicity, it is important to understand the life stability of the PWOUD population. To do this, we will utilize variables collected on methadone adherence and retention at each treatment visit (see Appendix A, Section A.1.1.1). We will summarize the longitudinal adherence profiles of each patient in each study arm. We will utilize appropriate clustering algorithms to identify and describe adherence patterns.

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