Safety of Direct Acting Antiviral Medications for Patients with Hepatitis C

NCT03423641

1/31/2018

Statistical Analysis Plan

Overview

We will use two different analytic approaches to answer the question of interest: a Poisson regression model and marginal structural modeling (MSM). These are described in more detail below. The simpler Poisson model is an extension of tabular rate of event analysis. The more complicated MSM model incorporates modeling of the treatment decision to more flexibly control for confounding by indication. For each outcome, we will only record the first date an outcome occurs. Also, each outcome will be modeled separately.

Detailed Description of Methods

Descriptive Statistics. We will calculate descriptive statistics at study entry. We will test for differences between the study sites using ANOVA, Chi-Square tests, and t-tests as appropriate. Similarly, we will test for differences between those who receive treatment and those who do not.

Poisson Regression Model. We have selected a Poisson regression approach to estimate case-mix adjusted outcome rates. This facilitates comparison to simpler tabular analyses. People may contribute multiple observations to the data set as covariates change over time.

Model:
$Y_{ij} \sim \text{Pois}(\lambda_{ij}T_{ij})$ Where Y_{ij} is assumed to be either 1 or 0 depending on whether the current outcome of interest occurred during the j^{th} exposure window of the i^{th} person, λ_{ij} is the expected daily rate of events for the the j^{th} exposure window of the i^{th} person and T_{ij} is the length of the j^{th} exposure window for the i^{th} person.

The j^{th} exposure window ends when one of the following occurs: end of study, end of membership, death, initial DAA Rx dispensed, a covariate changes (only if $\text{Trt}_{ij} = 0$), post-DAA follow-up time reached (only if $\text{Trt}_{ij} = 1$) 30, 90, or 180 days from the initial DAA prescription dispense, or current outcome of interest occurs.

As is common for a Poisson regression model, we let
$\log(\lambda_{ij}) = \beta_0 + \beta_1 \text{Trt}_{ij} + \vec{X}_{ij}\,\vec{\beta}$ where Trt_{ij} indicates whether the i^{th} individual transitioned to DAA at the start of their j^{th} exposure window. Once the initial prescription for DAA is dispensed, they transition from $\text{Trt}_{i(j-1)} = 0$ to $\text{Trt}_{ij} = 1$ for the remainder of the study. After the transition, to prevent mediation, no covariates are updated. $\vec{X}_{ij}$ is the vector of covariates for the the j^{th} exposure window of the i^{th} person.

The main parameter of interest, once exponentiated as $e^{\beta_1} = \text{IRR}$, can be interpreted as the ratio of the rate of an individual adverse event for people taking DAA compared to those who do not, after adjusting for possible confounders $\vec{X}_{ij}$.
Alternatively, we allow multiple treatment groups to be defined based on the total days supply of DAA received during the study.

Marginal Structural Modeling (MSM) can be thought of as the extension of propensity score weighting to treatment decisions over time. In propensity score modeling, the comparison and treatment arms are weighted to match the treatment of interest on baseline covariates. MSM extends this idea to modeling repeated opportunities to initiate treatment over time.

Following the notation of Robins et al. 2000, let V_i denote the vector of baseline static covariates, let L_{ik} denote the vector of time-varying covariates, and let A_{ik} denote the treatment group, and Y_{ik} denote the outcome for person i at time k.

We will fit the pooled logistic regression model for each outcome

$$\text{logit}(P_{ik}) = \beta_0 + \beta_1 a_{ik} + \vec{\beta}_V V_i$$

where $P_{ik} = P(Y_{ik} = 1)$ and each observation Y_{ik} will be weighted using the inverse probability of treatment weight (IPTW)

$$W_{ik} = \prod_{t=0}^{k} \frac{1}{P(A_{it} = a_{it} \mid a_{i(t-1)}, L_{it}, V_i)}.$$

Note that at each point of time we are weighting by the inverse of the probability of the treatment received rather than the probability of receiving DAA. While treatments can vary over time, once an individual receives DAA, they are in the DAA treatment group for the remainder of the study, so

$$P(A_{ik} = 1 \mid a_{i(k-1)} = 1, L_{ik}, V_i) = 1.$$

Weighting each observation using IPTW effectively creates a pseudo-population of subjects in which treatment is no longer confounded by V or L, thus $\hat{\beta}_1$ is an unbiased estimator of the the causal effect of treatment, if there is no unmeasured confounding.

For each time period k, we will fit the following logistic regression for the treatment conditional on all observed covariates.

$$\text{logit}\big(P(A_{ik} = 1 \mid A_{i(k-1)}, L_{ik}, V_i)\big) = \gamma_{0k} + \vec{\gamma}_L L_{ik} + \vec{\gamma}_V V_i.$$

Additional steps will be explored, such as cubic splines, to smooth β_{0k} over time. Also, since W_{ik} tend to be highly variable with small probabilities in the denominator leading to large weights, we will explore using the stabilized weight

$$SW_{ik} = \prod_{t=0}^{k} \frac{P(A_{it} = a_{it} \mid a_{i(t-1)}, V_i)}{P(A_{it} = a_{it} \mid a_{i(t-1)}, L_{it}, V_i)}.$$

Note that the numerator only depends on covariate values at baseline since it does not depend on L_{it}. The stabilized weight preserves unbiased estimation of the causal effects

of treatment while maintaining the same effective sample size as the original dataset. If some weights are still extreme, we will truncate the weights.

Similar to the treatment model, we will fit a logistic regression to model the probability of being censored. In order to obtain an unbiased estimate of the causal effect of treatment after accounting for both censoring and confounding, we will let each time period k in the outcome model be weighted by the combined weight

$$SW_{ik} \times SW_{ik}^{+}$$

where

$$SW_{ik}^{+} = \prod_{t=0}^{k} \frac{P(C_{it} = c_{it} \mid a_{i(t-1)}, V_i)}{P(C_{it} = c_{it} \mid a_{i(t-1)}, L_{it}, V_i)}.$$

We will perform diagnostics on the weights to determine if the weights satisfy the assumptions necessary for performing MSM. Violations will result in adjusting the treatment and censoring models as needed until the weights are able to satisfy the assumptions and account for observed confounding.

Although no observational study can claim to be free from confounding, the preliminary results from KPSC demonstrate that we can identify and account for the differences between groups in the methods that we are using. It is worth noting that at this point a randomized trial (the only sure way to avoid confounding) would be unethical. Further, this is a study of the safety of these agents so we anticipate finding either that there are safety problems or that there are not safety problems and either result, with an adequately powered study, will be useful to patients and their physicians who are making decisions about this treatment.

Missing data

At the KP sites the EHR is relatively mature. Based on our experience in the pilot study, we do not anticipate much missing data for typical data elements like treatments, demographics, vital signs, and lab values. We will run usual checks on variables to identify the rate of missing data for key variables and will identify variables with more than 5% of missing data. The OneFlorida sites carefully monitor the fields that are submitted with valid data. OneFlorida partners were asked to submit enhanced laboratory data with elements that are not included in the PCORnet Common Data Model. These enhanced laboratory data are necessary for the HCV study and others. UFHealth, Health Choice Network, Florida Hospital, and Tallahassee Memorial Hospital, which comprise the major providers within OneFlorida. We do not anticipate much missing data.

For most EHR based data elements we anticipate very low levels of missing data, typically less than 1%. For example, missing rates in the KPSC Hep C populations are: eGFR – 1.0%, Gender – 0.1%, Age – 0.1%, Race – 4.0%. Race imputation will be performed using the BISG algorithm from RAND. These values are already routinely calculated in the KP system. Other values will be imputed with mean value substitution. Sensitivity analysis will be performed by comparing to complete case analysis. Should

there be evidence that this missing data is influential full multiple imputation will be employed. Perhaps not best thought of as missing data there are variables that may be drivers of the treatment decision that may not have been collected. Potentially the most important of these is the MELD score of liver function with a missing rate of nearly 10%. The decision to collect the elements of the MELD score is likely a function of health status. It may be necessary to treat the decision to generate a MELD score as an endogenous process and use structural equation models to understand the effects of MELD scores on the treatment decision.

If more than trivial amounts of missing data occur, we will use multiple imputation and the corresponding analysis procedures to incorporate the estimated effects of imputation on coefficients and their standard errors. Disenrollment can be handled directly in the MSM model with an incorporated model for censoring.

Dropout will result primarily from a lapse in membership or death. Membership and death records are kept by the insurer and will be used to record and report dropout. As this is a retrospective analysis of data collected during patient care and stored in the EHR, reasons for missing labs and demographics will be unknown and not reported.

A complete case analysis will be compared to imputation based analysis.