HOTPIN Study Protocol

Facilitating In-Hospital OTP Intakes to Support Hospital-to-OTP Linkage

March 2026

NCT Number: TBD

Statistical Desing and Power

Using a novel staircase cluster randomized design with a Hybrid Type 2 approach, implement HOTPIN-IF at four diverse hospital sites and compare its effectiveness to usual care on hospital-to-OTP linkage and engagement.

Hypothesis: Compared to the usual care phase, the post HOTPIN-IF evaluation phase will have higher rates of **a)** 7-day OTP linkage (primary outcome), **b)** 30-day OTP engagement (secondary outcome). We will also assess **c)** OTP retention, **d)** acute care encounters and **e)** overdose deaths within the 90-days after the index discharge.

Approach. Using an incomplete stepped wedge cluster randomized cross-sectional trial design version known as a balanced staircase design[62], where sites are randomly assigned to time of implementation of HOTPIN-IF, we will test the effectiveness of HOTPIN-IF on hospital-to-OTP linkage, OTP engagement, and OTP retention, and acute care utilization and overdose death. We chose this design because 1) it allows for all sites to receive HOTPIN-IF which is important when there is a lack of clinical equipoise and it is desirable to receive HOTPIN-IF, 2) it facilitates conduct of the study related to logistical and personnel challenges with an external facilitator team leading HOTPIN-IF,[94] and 3) it efficiently targets periods with highest-yield.

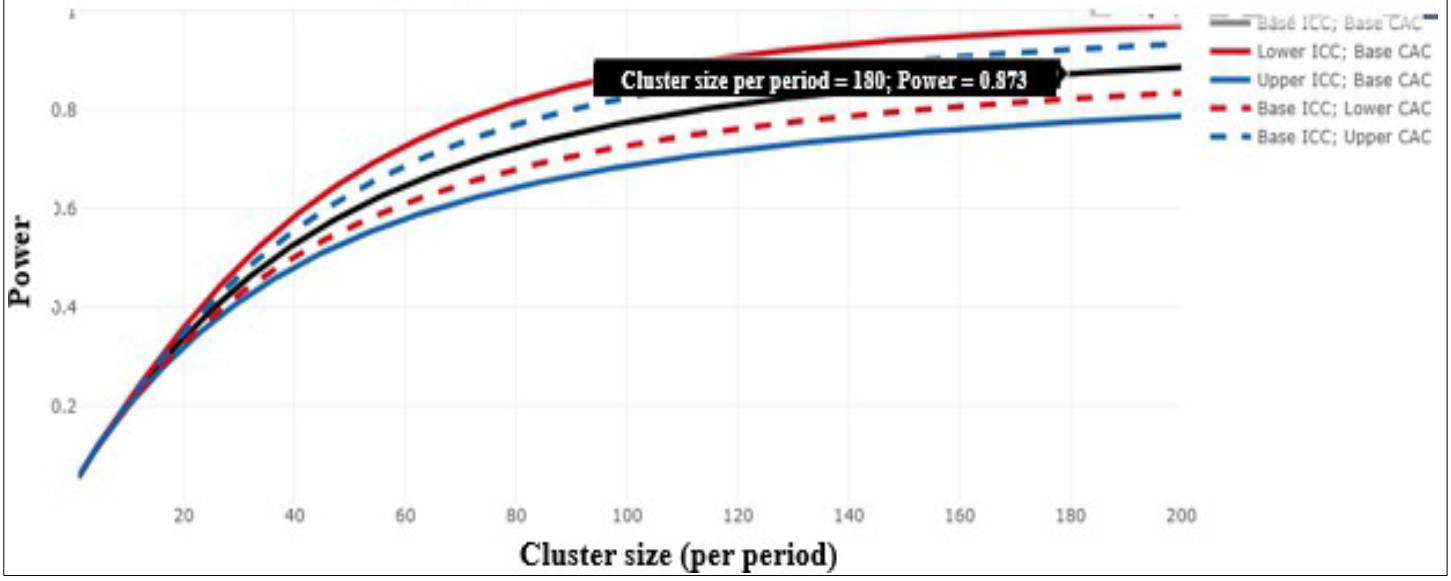
Study Design. Start dates of HOTPIN-IF will be randomly assigned across all four sites (Fig. 4). Because the staircase stepped-wedge design requires all sites to be at a common level of readiness prior to randomization, during the grant start-up phase, the four sites will attend a virtual meeting in which PI Calcaterra will review the updated 42 CFR Part 8 final rule[95] to provide an overview of the federal policy changes to support completion of in-hospital OTP intakes. Specifics of "how to" develop and implement these processes, i.e., HOTPIN clinical activities described in Fig. 1, will not be included in the presentation, but no information will be withheld if requested. Upon randomization, each site will begin a 12-month *usual care phase*, followed by a 6-month *HOTPIN-IF phase***,** followed by a 12-month *evaluation phase*, followed by a 3-month *maintenance phase* (Fig. 2, 3). HOTPIN-IF activities are described in Table 2. Study outcomes are measured at the individual patient level. **The primary outcome** is 7-day hospital-to-OTP linkage which will be measured during the *usual care phase* and the *evaluation phase*. Data collection will continue for 90 days following the index hospital discharge. We will report outcomes data consistent with CONSORT 2010 guidelines[96] and the CONSORT-Outcomes 2022 extension guidelines[97] for cluster-randomized trials modified for a stepped wedge design.[98]

Analytic Plan. *General approach.* We will generate descriptive statistics and visually evaluate variables to check for errors and outliers and to verify that the distributions of measures meet the assumptions of the planned statistical tests. We will evaluate whether study phases (*usual care* vs. *evaluation*; *usual care* vs. *maintenance*) are equivalent on patient, hospital, or OTP characteristics. For patient characteristics (e.g., sex, gender, race, ethnicity, housing status), hospital, and OTP characteristics that differ by group and/or are associated with outcomes, we will evaluate their inclusion as covariates. Results between unadjusted and covariate-adjusted analyses will be compared and any differences will be reported and discussed. Our study design and site-specific OTP affiliation is highly advantageous in that all of our primary, secondary and exploratory outcomes are obtained through records independent of patient participation and therefore should be complete and invulnerable to bias from attrition. We will conduct analyses in SAS and SPSS statistical packages. All tests will assume significance level alpha=0.05, two-tailed. For binary outcomes measured at a single time-point such as 7-day OTP linkage and 30-day OTP engagement, we will first evaluate treatment (*HOTPIN-IF, usual care*), site, and the treatment by site interaction overall difference among the two treatment conditions, HOTPIN-IF vs. usual care, for significance with logistic regressions via generalized linear mixed models accounting for variability from clustering of patients within sites and which allows for inclusion of covariates. If the treatment by site interaction is significant, we will subsequently conduct two-way comparisons between the two treatment groups at each site. If the interaction is non-significant, it will be removed and the model rerun to evaluate the treatment effect, adjusting for site. We will evaluate the after-study power that was achieved for each comparison.

Additional outcomes assessed at a single time point will be similarly evaluated with the appropriate statistical models (30-day OTP engagement and 90-day OTP retention with similar generalized linear logistic regressions; 90-day counts of ED and hospital encounters and 90-day counts of overdose deaths with generalized linear mixed models specifying negative binomial distribution and clustering of patients within sites) testing for differences between HOTPIN-IF and usual care.

Statistical Power. We expect to enroll approximately 15 patients per month on average for each site during the usual care and evaluation phases for a total of 1,440 patients enrolled during the two study phases (periods) across the four sites, i.e. 360 patients per cluster with 180 in each period. Using estimates from Tierney et al,[113] 40% of patients receiving usual care will link to OTP within 7 days. Assuming alpha significance level = 0.05 two tailed, SAS Proc Power was used to determine that 720 patients per treatment provides at least 96% power to detect a difference between treatment groups in OTP 7-day linkage of 10% or greater as significant without

Figure 5: Estimated power to detect as significant OTP 7-day linkage of 15% greater for HOTPIN-IF as compared to usual care from Shiny CRT Calculator specifying 4 sites each randomized to a 2-period sequence, 2-period decay correlation structure with estimated within-period ICC=0.02 (limits ± 0.01), and cluster auto correlation (CAC)=0.80, for staircase cross-sectional design



accounting for power reduction from clustering of patients within sites. Power was also estimated using the Shiny CRT calculator[114] that allows binary outcomes, specification of within period intra cluster correlation (ICC), between period ICC, and input of the staircase (i.e. incomplete stepped wedge) design proposed. Based on additional assumptions detailed in Figure 5, the expected cluster period size of n=180 provides 87% power to detect a minimum higher OTP 7-day linkage rate of 55% or greater from HOTPIN-IF as significant compared to the estimated usual care linkage rate of 40%.