Official Title of the study:

Intermittent Oral Naltrexone Enhanced With an Ecological Momentary Intervention for Methamphetamine-using MSM

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Statistical Analysis Plan

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Statistical Analyses

We will use generalized estimating equations (GEE) to estimate treatment effects on repeated study outcomes. Primary analyses will be by intention-to-treat (ITT). In prior trials, we had excellent visit retention and study completion. Nonetheless, in this high-risk population, missing data may be encountered.[215,216] We will conduct sensitivity analyses imputing all missing urine samples as positive, adjusting for baseline correlates of missingness, and using inverse probability of censoring weights.[217]

Specific Aim 1: *To determine the efficacy of ION vs. placebo in reducing meth use, as determined by the proportion of meth-positive urine tests.* As in our prior trial, a GEE Poisson model with robust standard errors will be used to compare weekly urine test results by treatment assignment; this provides easier-to-interpret risk ratios[218] rather than odds ratios. The treatment effect of ION vs. placebo will be modeled as linearly increasing and summarized by the between-group difference in means at 12 weeks, net of any baseline difference.

Minimum Detectable Effects (MDEs) with sample size: Based on the prior trial (93% retention), we estimate that 90% of participants will be retained at 12 weeks, and within-subject correlation will be 0.45. Under these assumptions, the study sample of 54 participants will have 80% power in 2-sided tests with a type-I error rate of 5% to detect net between-group differences in the reduction in urine positivity of ~24 percentage points, equivalent to a relative rate reduction of 32%. We have observed similar reductions on meth use in ITT and subgroup analyses in prior trials.[109] Therefore, we believe that the reductions in meth use we are powered to detect in this aim are reasonable to anticipate.

Specific Aim 2: *To determine the efficacy of ION vs. placebo in reducing meth-associated sexual risk behaviors.* We will use GEE Poisson models with robust standard errors to assess evidence that the intervention reduces HIV risk behaviors, including number of sex partners, and number of sex partners with whom meth is used.

MDEs: Using data from our prior trial on baseline means, within-subject correlation, and over-dispersion, we estimate that the study sample of 54 participants will have 80% power to detect ~46% net reductions in the numbers of sexual partners and ~67% reductions in partners with whom meth is used. In our Project iN study, we have observed statistically significant reductions on sexual risk outcomes ranging between 85%-89% among the treatment arm, compared to placebo.[109] Therefore, given the results from the prior trial, we believe that the reductions we are powered to detect in this aim are reasonable to anticipate.

Specific Aim 3: *To determine the efficacy of ION vs. placebo in increasing PrEP adherence among HIV-negative participants and ART adherence among participants living with HIV, as measured by serum drug levels and viral suppression rates.* We will use GEE Poisson models with robust standard errors to assess evidence that the intervention increases PrEP and ART adherence.

MDEs: Using the assumptions for loss to follow-up from Project iN for Aim 1, and informed by the within subject correlations of a PrEP adherence measure in the EPIC study[126] and of detectable viral loads among HIV+ participants in a Mirtazapine trial for MSM who use meth,[220] we estimate that the study sample of 54 participants will have 80% power to detect 10-19 percentage point increases in PrEP/ART adherence, depending on within-subject correlations and adherence levels in the reference group.