Persons who inject drugs (PWID) often experience stigma, which is defined as the social exclusion and dehumanization of individuals in an undesirable social category. A randomized controlled trial will be conducted to assess the effect of a stigma intervention targeted to help PWID cope with stigma. Patients will be recruited at 3 treatment addition clinics. They will be randomized 1:1 to either i) stigma intervention consisting of three 2-hour group sessions (stigma intervention), or ii) standard of care (control intervention). The primary outcome is overdose during the 12-month study period. The investigators expect that 15% of patients in the control group will experience an overdose in the 12 months following the intervention, but they hope that only 5% of patients in the stigma intervention group will experience an overdose event.

State the null hypothesis and the alternative hypothesis in both words and notation for the primary analysis. What is the clinically meaningful effect the investigators are hoping to detect?

H_0: $p_A = p_P$ The proportion of overdose is the same in the stigma intervention group and control group.

H_A: $p_A \neq p_P$ The proportion of overdose is not the same in the stigma intervention group and control group.

The investigators are hoping to detect a 10% decrease in proportion of overdose in the stigma intervention group compared to the control group.

Please compute and report the required total sample size to achieve 80% power for assessing superiority of the stigma intervention over the control intervention at the two-sided 0.05 level of significance. Adjust your sample size to account for potential loss to follow-up which is expected in 15% of the patients.

$$\frac{282}{1-0.15} = 332$$

A sample size of 282 total subjects, 141 per group, yields 80% power to detect a significant difference in proportion of overdoses of 10%, assuming risk of 15% in the control group and 5% in the stigma intervention group. To allow for 15% loss to follow-up, a total of 332 total subjects are needed.

Repeat the previous computation from with a 2:1 allocation ratio: report the total number of patients required to achieve 80% power. Adjust for an expected 15% loss to follow-up and report this total number of patients as well. Report how many additional patients are required for a 2:1 compared with a 1:1 ratio (under expected 15% loss to follow-up).

$$\frac{297}{1-0.15} = 350$$

A sample size of 297 total subjects yields 80% power to detect a significant difference in proportion of overdoses of 10%, using a 2:1 allocation ratio while assuming risk of 15% in the control group and 5% in the stigma intervention group. To allow for 15% loss to follow-up, a total of 350 total subjects are needed.

A secondary study outcome is change in stigma score from baseline to 12 months. Stigma score is measured in a scale ranging from 0 to 52 with higher scores being indicative of higher level of internalized stigma and lower self-esteem. Stigma score at baseline is expected to be 10 units with standard deviation of 8 units.

We expect to observe an average change in stigma score from baseline to 12 months of 1 in the control group. The study team thinks a clinically relevant difference in stigma score between the treatment and control groups is at least 3 units. State the null hypothesis that will be tested in this secondary analysis. Compute the power to reject the null hypothesis for the sample using the size you used previously (2:1 allocation ratio, accounting for loss to follow-up) at two-sided alpha=0.05. You may assume equal variability in the treatment groups (standard deviation of 8).

H_0: $\mu_A = \mu_P$ The average change in stigma score from baseline to 12 months is the same in the stigma intervention group and control group.

H_A: $\mu_A \neq \mu_P$ The average change in stigma score from baseline to 12 months is not the same in the stigma intervention group and control group.

Using a sample of 350 subjects in a 2:1 allocation ratio to detect a significant difference in change in stigma score from baseline to 12 months of at least 3 units, 90.8% power will be yielded.