Statistical Analysis Plan: Pooled analysis of SPOTLIGHT and STOP-IT

Final Version - October 3, 2016

The following represents a combination of analytic strategies from the two studies combining the raw data after completion of the SPOTLIGHT trial, projected to be in April 2016.

Comparison of randomized groups (rFVIIa vs placebo) – spot positive subjects:

The primary outcome of ICH growth within 24 hours will be compared between the two treatment groups by analyzing the final ICH volume on CT scan at 24 hours, adjusting for baseline ICH volume and time to study drug administration, by means of linear regression. The 24 hour ICH volume will be summarized for each group by descriptive statistics and the adjusted treatment effect and 95% confidence interval will be obtained from the regression model. Change and percent change in volume will be summarized with descriptive statistics to allow comparison with other studies. Similar analyses will be performed for intraventricular hemorrhage volume and total volume (ICH plus intraventricular hemorrhage). A fixed effect representing study will be retained in all models to account for any underlying study differences. For consistency the ICH size as calculated by volumetric analysis will be used for all analyses.

As the inclusion criteria for the two studies were different, an analysis will be performed on a subset of the total population adhering to the most conservative of the combined inclusion criteria. Other potential analyses, examine interaction of group and: onset-to-treatment time (<3 vs. >3 hours); baseline ICH volume (<30 vs. >30 ml)

The frequency of adverse events will be reported by treatment group. The sample is small and adverse events are not expected to be common, and expected frequencies low.

The proportion of patients in each group achieving a 90-day modified Rankin score 5-6 (death or severe disability) will be compared in an adjusted analysis. Multiple logistic regression will be used to assess the odds of poor outcome in the rFVIIa vs placebo group, adjusting for study to control for any differences between studies, such as slightly different eligibility criteria. Potential covariate/confounders would be age, baseline ICH volume, onset to treatment time, presence of intraventricular hemorrhage, Glasgow Coma score, and pre-stroke Rankin score. Since the sample size is not large the number of outcome events are anticipated to be low, thus adjustment for other variables in addition to study is likely to produce an unstable or overfit model. Therefore, the most important variables (from literature) will be reviewed in terms of their distributions and those possessing sufficient variability will be adjusted for; time and volume are currently considered as important to consider. Similar analysis will be performed for mortality and the other clinical scales. We will test the proportional odds assumption and only proceed with reporting this approach if the assumption is not violated.

Examination of the spot sign as an indicator of hematoma growth:

This analysis will use data from STOP-IT patients without a spot sign and the subjects randomized to placebo in SPOTLIGHT and STOP-IT trials. The same regression approach will be used as that comparing the randomized groups above; that is ICH growth within 24 hours will be compared between the two groups (with versus without the spot sign) by analyzing the final ICH volume on CT scan at 24 hours, adjusting for baseline ICH volume and time from stroke onset to scan, by means of linear regression.

The proportion of patients the spot positive versus spot negative groups achieving a 90-day modified Rankin score 5-6 (death or severe disability) will be compared in an adjusted analysis. Multiple logistic regression will be used assess the odds of poor outcome in the spot positive versus spot negative group. It is not possible to adjust for study in this analysis as all of the spot negative patients will only come from the STOP-IT study. However it may be possible to adjust for age and baseline ICH volume. Other possible adjusting factors would be presence of intraventricular hemorrhage, Glasgow Coma score, and pre-stroke Rankin score, however the same limitations/reservations apply as above, due to small number of events anticipated so a similar approach to variable selection will be employed. Similar analyses will be performed for mortality and the other clinical scales. A shift analysis across the full range of mRS scores will be performed using the methodology of Saver to estimate the number of patients needed to treat for 1 additional patient to improve by 1 or more levels of disability on the mRS.

General for all analyses:

Missing data: If the study subject is lost to follow-up, then the worst score short of death for modified Rankin and Barthel at 90 days will be assigned. These assumptions are consistent with the handling of missing outcome data in the NINDS rt-PA Stroke Study. In addition, all analyses will be repeated excluding the cases with missing data to check for potential bias. Missing covariate data will be estimated using multiple imputation.

We shall not be adjusting for multiple comparisons